The impact of genes by childhood adversity interaction on the clinical and social outcomes of psychosis

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The history of mankind is the history of ideas.

Luigi Pirandello

ABSTRACT

A history of childhood adversity is associated with adult psychotic disorder but it is not known why only some exposed individuals go on to develop psychosis and what their outcomes are. This study aimed to explore the association between specific forms of childhood adversity and the presence, and one-year outcomes, of psychosis and the interplay with familial liability, candidate genes and polygenic risk scores. Data on 285 first-presentation psychosis cases and 256 geographically-matched controls drawn from the Genetic and Psychosis (GAP) study was utilised. Childhood adversity exposure was assessed using the Childhood Experience of Care and Abuse Questionnaire (CECA.Q), family psychiatric history with the Family Interview for Genetic Studies (FIGS) and genetic information was extracted from blood and buccal samples. The Psychiatric and Personal History Schedule (PPHS) and the Global Assessment of Functioning Scale (GAF) were completed from clinical records to ascertain clinical and social outcomes in the cases over the first year since initial presentation to psychiatric services for psychosis.

Separation from mother or father (for at least 6 months) before the age of 17 years demonstrated the most robust association with psychotic disorder after controlling for all confounders including parental history of psychosis (Adj.OR=2.22, 95% CI: 1.52-3.27, $p<0.001$) and was also associated with longer psychiatric admissions (Adj.OR=2.45, 95% CI: 1.06-5.66, $p=0.035$) and non-compliance with antipsychotic medications (Adj.OR=2.34, 95% CI: 1.11-4.92, $p=0.026$) at one-year follow-up. There was no evidence for interaction between any type of childhood adversity and either family psychiatric history or candidate genes in relation to either the presence or one-year outcomes of psychosis. However, a pilot study on a subsample of 86 psychosis cases and 110 community controls of Caucasian parentage revealed an interaction between a schizophrenia polygenic risk score and parental separation, parental loss and sexual abuse for the presence of psychosis (all $p<0.001$).

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INTRODUCTION

Science is built up with facts, as a house is with stones.
But a collection of facts is no more a science than a heap of stones is a house.

Henri Poincaré, La science et l'hypothèse, 1908

When the term psychosis[1] was introduced in the psychiatric literature, in the beginning of the 19th century, it was used to refer to mental disorders with identifiable organic causes (Bleuler, 1950; Haslam, 1809; Pinel, 1798). Since that time, several hundred thousand publications pertaining to psychosis have described thousands of discrete findings (Wyatt, 1988). However, its aetiology and pathophysiology remain relatively obscure. In fact, going back to Poincaré's quotation, the question is: which of these findings can be considered established and exactly what do these facts tell us about the nature of psychosis?

Twin, family, and adoption studies, all clearly support a major role for genes in schizophrenia (Riley et al., 2005). Furthermore, recent advances from large-scale collaboration in genome-wide association studies (GWAS) have demonstrated that rare copy number variants (CNVs) increase schizophrenia risk substantially and to a greater extent than individual common risk alleles (Grozeva et al., 2010; Guha et al., 2013; Lee at al., 2012; Malhotra et al., 2012; Ripke et al, 2013). On the other hand, increasing evidence suggests that early environmental exposures influence psychosis expression even in the presence of strong genetic predisposition (Husted et al., 2012). Environmental factors linked to a higher likelihood of developing schizophrenia include obstetric complications (Cannon et al., 2002), living in urban areas (Allardyce & Boydell, 2006; Heinz et al., 2013), history of migration (McGrath et al., 2004), being part

[1] From the Greek words psukhē (soul, mind) and osys (abnormal). Oxford English Reference Dictionary (1996), Oxford: Oxford University Press.

of a minority ethnic group (Morgan et al., 2010), cannabis use (Arseneault et al., 2004; Henquet et al., 2005; Minozzi et al., 2010), and experience of adversity in childhood (Matheson et al., 2013; Morgan & Fisher, 2007; Varese et al., 2012) and adulthood (Beards et al., 2013).

Given that research has shown that both nature and nurture likely play an important role in the aetiology of psychotic disorders (van Zelst, 2008), the field has seen the progressive replacement of mono-causal models by multidisciplinary perspectives which integrate psychosocial interactions as well as neurobiological predispositions. Therefore, today the accepted idea is that the aetiology of psychosis is complex and requires explanatory models that include gene by environment interactions (Shah et al., 2011). However, it is only in the past decade that investigators have seriously begun to explore how exactly genetic and environmental elements interact to cause psychosis (Benzel et al., 2007; Caspi et al., 2005; Cheng et al., 2008; Cougnard et al., 2007; Hanninen et al., 2008; Krabbendam & van Os, 2005; Mathew et al., 2007; Nicodemus et al., 2007; Sei et al., 2007; Tienari et al., 2004; Zammit et al., 2007).

Genetic factors and gene-environment interactions together have been shown to contribute over 80% of the liability for developing schizophrenia (Uher, 2014). Although it appears that our understanding of the causation of psychosis has substantially increased over the past two decades, what we can confidently assert is that both genetic and environmental factors are important, but exactly which specific exposures and how they interact to cause schizophrenia is still not understood at this time (European Network of Schizophrenia Networks for the Study of Gene-Environment Interactions, 2008). Thus, there is an obvious gap in the literature between “findings” and “understanding” for research exploring the interaction between genetic and environmental factors in the onset and course of this disorder.

Aims

A lifetime history of childhood adversity is associated with increased risk for psychosis (Varese et al., 2012a) but it is not known why only some individuals exposed to early stress go on to develop psychosis and what their outcomes are. Moreover, only a few studies have assessed the interactions between genes and childhood adversity in psychotic disorders. Furthermore, research to date has not given due attention to the impact of gene by childhood adversity interactions on the clinical and social outcome of psychosis.

This project builds upon a large first-episode psychosis case-control study followed over a one-year period and proposes to extend previous work by investigating the influence of the interaction between genes and childhood adversity on increasing the risk of psychosis and the clinical and functional one year outcomes of psychosis patients.

Using a case-control design, the principal aims of this research are:

1. To investigate the reported prevalence of different forms of childhood adversity in first-presentation psychosis cases compared to geographically-matched controls (Chapter 4).
2. To explore whether childhood adversity has an effect on the clinical and functional one year outcome of psychosis patients (Chapter 4).
3. To explore whether associations between childhood adversity and psychotic disorder are confounded or moderated by familial proxy genetic risk (Chapter 5).
4. To conduct an investigation into the potential interaction between childhood adversity and functional candidate genes in the onset and course of psychosis (Chapter 6).
5. To conduct a preliminary exploration of whether the impact of childhood adversity on the onset and one year clinical and functional outcomes of psychosis is moderated by polygenic risk factors (Chapter 7).

Definition of research terms

Psychosis

The term psychosis is currently used to describe a mental state characterised by some loss of contact with external reality and by disturbances to the normal processes of thought or perception. People with psychosis may also experience disruptions to cognitive, emotional and behavioural functioning.

In order to make a diagnosis of a psychotic disorder three kinds of psychotic symptoms are taken into consideration: delusions, hallucinations and disorders of thought (American Psychiatric Association, 2013). A delusion is a false belief that is firmly held on inadequate grounds, is not affected by rational argument or evidence to the contrary, and is not a conventional belief that the person might be expected to hold. Some of the most common forms of delusional belief in psychoses are delusions of 'reference'. These are beliefs that object, events or people have a special significance for the patient. 'Nihilistic' delusions have a deeply pessimistic nature; e.g. they can include a belief that one is about to die or that the world is doomed or involve a mistaken conviction that some person or something no longer exists. People with 'grandiose' delusions instead hold beliefs of exaggerated self-importance, based on a conviction that one is extremely wealthy, endowed with unusual abilities or that one is a very special person (Murray & Dean, 2008).

A hallucination is the perception of something as real (e.g. a voice or an image) which occurs in the absence of an external stimulus to the sense organs and it is usually experienced as originating in the outside world (or sometimes within one's own body). Probably the most common types of hallucination are those in the auditory modality (e.g. voices, music, tapping, laughs). Hallucinations in other sensory modalities also occur: visual hallucination, people see images that others cannot see e.g. flashes, shadows or coloured lights; olfactory hallucinations are experienced as odours which other people cannot smell while tactile hallucinations relate to claims made by people that they are

being touched when there is no person or no thing around to do the touching (Murray & Dean, 2008).

Disorders of the normal processes of thought include: 'loosening of associations' (a decrease in the normal structure of thinking), 'flight of ideas' (the patient's thoughts and conversation move quickly from one to another so that one train of thought remains incomplete after another appears) and disorders of the stream of thought (a rapid increase in the volume of thoughts generated which pass very quickly through the mind; Murray & Dean, 2008).

Moreover, the classification of psychotic disorders depends upon symptom duration and the presence or absence of prominent affective symptoms. According to the ICD-10 classification system (World Health Organization, 1992a), the criteria for a diagnosis of schizophrenia are met if psychotic symptoms have been present for at least one month; this compares with the DSM-V, which requires a minimum duration of six months (American Psychiatric Association, 2013). Patients who receive a diagnosis of schizophrenia often present impaired performance on tests of IQ, reasoning, language and memory (Trotta et al., 2014; Wongupparaj et al., 2014).

Lifetime prevalence of psychotic disorders is estimated to be between 0.5% and 1% (Jablensky et al., 1992). A systematic review reported that the incidence rates of schizophrenia range from 7.7 to 43.0 per 100.000 with a worldwide variation up to fivefold (McGrath, 2006). Moreover, higher rates have been found depending on use of a broader diagnostic definition (Perälä et al., 2007), male gender (McGrath, 2006), urbanicity (Mortensen et al., 1999), ethnicity and history of migration (Cantor-Graae & Selten, 2005). Therefore, it seems that differences in the distribution among populations, and over time, of the risk factors implicated in the aetiology of both psychotic symptoms (Johns et al., 2004) and clinical psychotic disorders (McGrath, 2006), might help to explain the variation in their incidence rates by place and time. Considering this, diagnostic classification systems have been revised for the recent release of the DSM-5 (American Psychiatric Association, 2013) and in the near-future, the ICD-11.

Specifically, the DSM-5 has offered the possibility of complementing the existing categorical classification with dimensions (Demjaha et al., 2009; van Os et al., 1999).

A dimensional classification considers the psychoses, such as schizophrenia and bipolar disorders on a continuum of liability (Taylor, 2002), challenging the Kreapelinian view that schizophrenia and affective disorder are biologically distinct. Moreover, within this approach, experiencing symptoms of psychosis such as delusions and hallucinations is not inevitably associated with the presence of psychotic disorder. The latter is thought to be dependent on symptom factors such as intrusiveness, frequency and psychopathological co-morbidities on the one hand, and personal and cultural factors such as coping, illness behaviour, societal tolerance and the degree of associated developmental impairment on the other (Johns & van Os, 2001). Thus, even though the prevalence of the clinical disorder is low, the prevalence of the psychotic symptoms can be much higher (van Os et al., 2009).

However, data from follow-up studies indicates that approximately 75-90% of developmental psychotic experiences are transitory and disappear over time (van Os et al., 2009). Nonetheless, there is evidence, that transitory developmental expression of psychosis (psychosis proneness) may become abnormally persistent (persistence) and subsequently clinically relevant (impairment), depending on the degree of environmental risk the person is additionally exposed to (van Os et al., 2009). Therefore, the psychosis proneness–persistence–impairment model proposes that genetic background factors impact on a broadly distributed and transitory population expression of psychosis during development. A poor clinical and functional prognosis, in this model, is predicted by environmental exposure interacting with genetic risk (van Os et al., 2009).

Nevertheless, the conceptualization of psychosis in this thesis is determined by the nature of the sample being used and the measures completed upon them. Hence, the subsequent chapters focus mainly on individuals

presenting to psychiatric services for the first time with evidence of psychotic symptoms that fulfil the diagnostic criteria from the International Classification of Diseases [ICD-10 (codes F20-F29 and F30-F33)]; World Health Organization, 1992a), determined using data from the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; World Health Organization, 1994). Full information is provided in the Methodology Chapter (3).

Childhood adversity

About a third of the general population has a lifetime history of childhood adversity (Kessler et al., 2010) and it remains a major public-health and social-welfare problem in high income countries (Gilbert et al., 2009). The term childhood adversity is a broad concept which includes child maltreatment (all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation), peer victimization (e.g. bullying), experiences of parental loss and separation, war-related trauma, natural disasters and witnessing domestic or non-domestic violence (Butchart et al., 2006).

It is striking to think that, so far, there are no systematic methods of classifying adversity; so different criteria are employed for the severity, frequency, persistence and age of exposure to such experiences making comparisons of findings between different studies or research groups very difficult (Cicchetti, 1994; Manly et al., 1994). For example, findings from nationally representative samples of young adults aged 18–24 years, asked retrospectively about childhood adverse experiences, showed decreases during ten years in reports of physical abuse (from 13.1% in 1998–99 to 9.8% in 2009), sexual abuse (6.8% to 5%), and verbal abuse (14.5% to 6%) (Radford et al., 2012). In contrast, Gilbert and colleagues found no changes in trends in childhood adversity, suggesting that these figures could alternatively indicate a decline in overall prevalence accompanied by an increase in recognition and recording (Gilbert et al., 2012).

Over the past 30 years there has been increased responsiveness to childhood adversity on many Western countries. Expansion of definitions of adversity to include emotional abuse and witnessing of intimate partner violence, and changing thresholds for moving from recognition to recording and action, which consequently might increase the number of reported cases throughout the system (Gilbert et al., 2012).

Existing research of how childhood adversity is changing in developed countries is conflicting. Studies that rely on officially recorded or substantiated adversity measure only a small part of the bigger picture. Most childhood adversity is hidden and not recognised by professionals dealing with children; alternatively, it might be that professionals in contact with children consistently report to child protection agencies only a proportion of children whom they recognise as being maltreated (Butchard et al., 2006; May-Chahal & Cawson, 2005). Instead, self-reported or parent-reported incidents of adversity probably come closest to measurement of the occurrence of adversity, although these studies might still underestimate the severity of the problem (Janson et al., 2007; Leeb et al., 2008; Nelson et al., 2002).

For the purposes of this thesis, six forms of childhood adversity captured by the Childhood Experience of Care and Abuse Questionnaire (CECA.Q) (Bifulco et al., 2005) will be investigated in relation to psychosis, namely:

- Disrupted parental arrangements (3 or more lasting at least a year each)
- Taken into local authority care (any length of time)
- Death of mother or father
- Separation from mother or father (for at least 6 months)
- Physical abuse by the main mother and father figures (not necessarily the biological parents)
- Sexual abuse by any adult or an individual at least 5 years older than the recipient

Childhood experiences must have occurred before the age of 17 years. Every childhood experience section of the CECA.Q begins with screening questions and

then positive responses are followed up with more detailed questions. The CECA.Q elicits concrete examples of adverse experiences, and a guide has been published to score the severity of the responses in a standardised manner (Bifulco et al., 2005). In order to minimise false positives the most conservative published cut-off points have been utilised to estimate the prevalence of adversity in this thesis (see Methodology Chapter 3).

Thesis outline

This thesis comprises a total of eight chapters and the composition of each of these is briefly described below:

- Chapter 1 is an introductory chapter on the impact of childhood adversity on psychosis onset and a literature review on its association with clinical and social outcomes.
- Chapter 2 provides an overview on gene-environment correlation and gene by environment interaction in the onset and course of psychosis.
- Chapter 3 outlines the methodology of the Genetics and Psychosis (GAP) study. This includes a detailed description of the CECA.Q (Bifulco et al., 2005), which was utilised to assess childhood adversity in this study. The final section of this chapter states the candidate's contribution to the work within this thesis.
- Chapter 4 contains the main results of the thesis, specifically the association between childhood adversity and (i) psychosis onset (Section 4.1), and (ii) clinical and social outcomes over one year follow-up (Section 4.2).
- Chapter 5 provides results on the interplay between childhood adversity and family history of mental illness on psychosis onset (Section 5.1) and one-year outcomes (Section 5.2).

- Chapter 6 reports results of candidate genes, *COMT*, *AKT1* and *FKBP5*, x childhood adversity interactions in psychosis (Section 6.1) and its outcomes (Section 6.2).
- Chapter 7 contains preliminary results from a pilot study exploring the interaction between a Polygenic Risk Score for psychosis and childhood adversity on psychosis onset and outcomes.
- Chapter 8 summarises the findings presented in the preceding chapters together with a discussion of their clinical implications and directions for future research.

Distinct and original contributions

The original idea for this project was conceived by Professor Sir Robin Murray and Dr Helen Fisher (Institute of Psychiatry, Psychology and Neuroscience, KCL). I developed this into a full PhD proposal and obtained funding from the Psychiatry Research Trust. Data collection for my PhD forms part of a larger study of first-episode psychosis, as detailed above. Although I did not directly contribute to the data collection of the GAP baseline study, I was involved in the training for the computerised Operational Criteria diagnostic system (OPCRIT; McGuffin et al, 1991) and completed assessments for baseline diagnosis using OPCRIT diagnostic system.

Most of my PhD activity has been focused on completing one year follow-up assessments of the psychosis patients from clinical records. I was responsible for assessing the clinical and social outcomes of GAP study patients at one year from the first contact with psychiatric services for psychotic disorder. I have also been involved in the training on the follow-up assessment and established the inter-rater reliability. My specific contribution to this study was to:

1. Complete assessment for baseline diagnosis using OPCRIT diagnostic system for a total of 10 GAP patients.

2. Trace a total of 182 GAP patients over a period of one-year from first-contact for psychosis with SLAM mental health services.
3. Independently complete a total of 119 assessments for one-year follow-up from hospital records, using the Follow-Up Personal and Psychiatric History Schedule (FU-PPHS) and the Global Assessment of Functioning (GAF) Scale.

I entered all the follow-up variables relevant to my thesis and checked the baseline data entered into SPSS databases thoroughly for errors and inconsistencies. During the third year of my PhD, I was awarded a King's Partnership grant to visit the Genome Research Center at University of Hong Kong, where I deepened my understanding of GxE interaction models under the supervision of Professor Pak C. Sham.

I was responsible for conducting all the analyses of data presented in this study following guidance from Dr Helen Fisher and Professor Sir Robin Murray. I wrote this thesis in its entirety under their supervision.

To date this work has generated 3 peer-reviewed journal papers, 4 abstracts and 5 international conference presentations. A detailed list of the publications is provided in Appendix I, followed by copies of the journal articles (Appendices II-V).

Furthermore, the work which is believed to be original and contributory to achieve the objectives can be summarised as follows:

- Exploration of the association between different types of childhood adversity with clinical and social outcomes in a sample of first-presentation psychosis patients over a one-year period (Section 4.2).

- Investigation of the interaction between familial liability for psychosis and different types of childhood adversity in discriminating between psychosis patients and unaffected controls (Section 5.1).

- Exploration of the interplay between familial liability for mental illness and childhood adversities on clinical and social outcomes in the year following first presentation to mental health services (Section 5.2).
- Investigation of the interaction between the main putative susceptibility genes and different types of childhood adversity in the development of psychotic disorders (Section 6.1) and one-year outcomes (Section 6.2).
- Pilot work on the interaction between different types of childhood adversity and polygenic risk score on the presence of psychotic disorder (Chapter 7).

CHAPTER 1 – Literature review of association between childhood adversity, onset and outcome of psychotic disorder

My heart leaps up when I behold
A rainbow in the sky:
So was it when my life began;
So is it now I am a man;
So be it when I shall grow old,
Or let me die!
The Child is father of the Man […]
William Wordsworth, My heart leaps up, 1802.

Childhood adversity and onset of psychosis

A century after the English poet William Wordsworth wrote the above lines, Sigmund Freud formulated his psychoanalytic developmental theory (Freud, 1896). Recalling the expression "*The Child is father of the Man*", Freud wanted to underline the impact of early experiences on adulthood. From his pioneering discoveries, trauma has been the focus of further investigation from a psychoanalytic perspective. In this perspective, the subject's vulnerability is always the result of the inevitable interplay between objective and subjective, external and internal reality (Ferenczi, 1933). However, only in the last few decades has substantial evidence accumulated from a non psychoanalytic perspective to show that a variety of adversities experienced in childhood are associated with psychiatric disorders in adulthood.

A British national survey conducted among 2,869 young adults aged 18–24 years reported that severe maltreatment had been experienced by 16% of the sample (May-Chahal & Cawson, 2005); this was associated with poorer emotional wellbeing, self-harm, suicidal ideation and delinquent behavior (Radford et al., 2011). Moreover, childhood adversity has been claimed to

predict over 32% of all psychiatric disorders (Green et al., 2010) including depression, anxiety disorders, post-traumatic stress disorder (PTSD), eating disorders, substance misuse, sexual dysfunction, personality and dissociative disorders at all life-course stages (Kilpatrick et al., 2003; Ruchkin et al., 2007; Wasserman & McReynolds, 2011; Lobbestael et al., 2010).

Recently, increasing interest has been shown in the relationship between child maltreatment (e.g., sexual abuse, physical abuse, emotional/psychological abuse and neglect), peer victimization (e.g., bullying), parental loss (via death and separation), and risk of experiencing psychotic symptoms in adolescence as well as full-blown psychotic disorders in adulthood (Bebbington et al., 2004; Morgan et al., 2007; Fisher et al., 2010; Arseneault et al., 2011; Kelleher et al., 2013; Trotta et al., 2013). There are a large number of studies of psychiatric inpatients, and of outpatients in which a majority have a psychotic disorder, that suggest the prevalence of childhood trauma in these populations is high (Morgan & Fisher, 2007, Schäfer & Fisher, 2011; Bebbington et al., 2004). Large-scale general population studies hint at a potentially causal relationship, as the effect becomes stronger with cumulative exposure (van Winkel et al., 2008b; Read et al., 2005).

Moreover, studies focusing on the possible influence of the type of trauma experienced, reported stronger associations between abuse and psychosis, compared with neglect (Heins et al., 2011; Shevlin et al., 2007). However, there is now emerging evidence that childhood adversities are related to specific symptoms of psychosis and schizophrenia, particularly hallucinations and paranoid delusions (Bentall et al., 2014; Read et al., 2003; Bebbington et al., 2004; Matheson et al., 2013) and, differently from psychosis diagnosis, the association remains significant regardless of the type of childhood adversity (i.e. sexual abuse and growing up in foster care) (van Nierop et al., 2014c).

These findings have also been summarized in a recent quantitative review and meta-analysis of the available empirical literature which reported a strong significant association between childhood adversity and increased risk for

psychosis (OR=2.78), regardless the specific type of exposure and study design (Varese et al., 2012). However, although several reviews and meta-analyses have synthesized and quantified the magnitude of the association with onset of psychosis (Morgan & Fisher, 2007; Bendall et al., 2008; Schäfer & Fisher, 2011), the potential long-lasting impact of traumatic early experiences on the clinical and social course of psychotic disorder is currently unclear.

Follow-up studies on first-episode psychosis reported that between around 20% and 30% of all cases experienced a continuous course (Harrison et al., 2001; Möller et al., 2010; Morgan et al., 2014a; Wiersma et al., 1998) and poor social outcomes over time (Hegelstad et al., 2012; Morgan et al., 2014a; White et al., 2009). Therefore, identifying predictors of both clinical and social outcomes that can be targeted to improve trajectories of psychoses is the next challenge.

Potential pathways from adversity to psychosis onset

Psychological mechanisms

The aetiology of psychosis may be better understood by considering several layers of explanations, including psychological as well neurobiological. The latter will be discussed in the next paragraph, while I will focus here on the individual psychic experience. In the last 20 years, a consensus has been developed that cognitive and affective changes underlie symptoms of psychosis (Garety et al., 2001; 2007). Cognitive models of psychosis postulate that dysfunctional appraisals about the self and the world might develop following adverse childhood experiences, such as hostile attributions of others' intentions, negative self-perceptions and lack of personal control over events, and these could be related to the onset and maintenance of psychotic phenomena (Campbell & Morrison, 2007; Fowler et al., 2012; Garety et al., 2001). Indeed, both low self-esteem and an external locus of control have been reported to form an indirect pathway between adversity in childhood and psychotic-like symptoms in early adolescence in a large prospectively assessed UK birth cohort (Fisher et al.,

2013). Moreover, exposure to adversity might influence appraisals of hallucinations by promoting the formation of negative beliefs about voices (Andrew et al., 2008; Chadwick & Birchwood, 1994; Morrison et al., 2004).

Appraisal of psychotic symptoms, such as auditory hallucinations and persecutory delusions, as powerful and controlling is also linked to depressed mood (Birchwood et al., 2003; Green et al., 2006) as well as to suicidal ideation (Fialko et al., 2006). Therefore, trauma and adversity affect both information and emotional processing (Kuipers et al., 2006). Negative perceptions of the self, anxiety, and depression have been found also to partially mediate associations between early adversity and emergence of psychotic experiences (Fisher et al., 2012). Studies have also shown that cognitive factors and depression may be involved in the maintenance of psychotic symptoms over time (Vorontsova et al. 2013), though this has not been explored specifically in the context of adversity exposure.

A certain degree of specificity is present for the impact of different kinds of adversity on emotional and cognitive systems. For example, psychological abuse and humiliation leads to reduced self-esteem (Briere, 1990), events that involve an immediate threat and from which escape is not possible are particularly potent with respect to dissociation (Griffin et al., 1997; van Der Kolk & Fisler, 1995), whereas events that disrupt early attachment relationships will affect attachment styles and hence interpersonal relationships in the future (Bowlby, 1965).

Decreasing interest has been focused on the role of expressed emotions within the family environment as a predictor of psychosis onset and poorer patient outcome (Finnegan et al., 2014). Carers' emotional reactions and behaviors towards the child, especially if characterized by high levels of criticism, hostility and/or emotional over involvement (Vaughn & Leff, 1976), are likely to be internalized and create mental representations of the self as vulnerable and the world as threatening, along with a pattern of affective instability (Marwaha et al., 2014). Therefore, therapeutic interventions, both at an individual and

familial level, have been suggested to first focus on the engagement of the patient to create a solid therapeutic alliance that will last throughout the treatment (Kuipers et al., 2006). This protective environment is likely to be perceived by the patient as a safe place where reappraisal of negative beliefs (Green et al., 2006), negative schemas about the self, other people and the world (Fowler et al., 2006; Freeman, 2007) and reasoning biases characterized by inflexibility and inability to generate alternative explanations (Garety et al., 2013a; 2013b; Falcone et al., 2015) could be gradually challenged and acknowledged. More than the specific therapeutic approach (Jauhar et al., 2014), psychological factors such as warmth, kindness and the instilling of hope are intrinsic elements of all forms of psychotherapy without which nothing beneficial can be expected to happen (Bentall, 2009) and they are likely to assume particular importance for those people that experienced early adversity.

Biological mechanisms

Another way that exposure to adversity during childhood could lead to development of psychosis in adulthood is through physiological mechanisms. The hypothalamic pituitary adrenal axis (HPA) is one of the main biological systems involved in the stress response (Charmandari et al., 2003) and has also been postulated to mediate the relationship between stress and psychotic disorders (Walker et al., 2008). In response to stressors, activation of the HPA axis results in release of corticotrophin-releasing hormone (CRH) from the hypothalamus. Early chronic stress leads to an initial increased cortisol secretion, with an initial hyper-activation of the HPA system followed by a state of hyporeactivity as a way of adaptation after sustained exposure to ACTH (McCrory et al., 2011). Increased cortisol levels and evidence of reduced negative feedback of the HPA axis, have been reported in subjects experiencing attenuated psychotic symptoms and those developing frank psychosis (Thompson et al., 2007).

Stress in early life has been associated with insufficient glucocorticoid signalling in adulthood, possibly affecting inflammation processes. A longitudinal-

prospective study linking the exposure to childhood maltreatment in the first decade of life to clinically significant biomarkers of inflammation in adulthood reported that maltreated children showed a significant and graded increase in the risk for clinically relevant C-reactive protein levels 20 years later (Danese et al., 2007).

Moreover, adults who reported experiences of childhood maltreatment showed a reduced ability of glucocorticoid signaling to control the hypothalamic-pituitary-adrenal axis response to a psychosocial stress test (Heim et al., 2000). Specifically, it appears that childhood maltreatment may lead to atypical responsiveness of the HPA axis to stress, which in turn predisposes to psychiatric vulnerability in later life (McCrory et al., 2011; van Goozen & Fairchild, 2008). In fact, previous research reported that stress sensitivity and activity of the HPA axis secretion may be relevant to the development of psychiatric vulnerability in adulthood and the expression of psychotic disorders such as schizophrenia (Rosenthal, 1970; Walker & Diforio, 1997). In 1997, Walker et al. proposed a "neural diathesis-stress model": the HPA axis triggers a cascade of events leading to a dysfunction of neural circuits that are linked to the expression of psychotic symptoms. Elevated cortisol levels, pronounced reductions in volume of the hippocampus, activation of dopaminergic circuits and the impact of pre- and post-natal factors in the etiology of schizophrenia support the hypothesis of a link between childhood adversity, HPA activity, and psychosis (Walker & Diforio, 1997). In this model the HPA axis mediates the relationship between early stress and risk for psychotic disorders, and it also represents a nonspecific moderating system altering the expression of neural circuitry dysfunction that underlies psychosis (Walker et al., 2008).

Recent research has suggested that elevated basal salivary cortisol secretion might have predictive value for development of psychotic disorder (Walker et al., 2010; Mondelli et al., 2011; 2010a; 2010b). Neuroimaging (Garner et al., 2005; Soliman et al., 2008) and preclinical (Lodge & Grace, 2006) studies support the specific idea that cortisol secretion is an easily assayed biological

correlate of stress sensitivity that is hypothesised to play a role in the generation of positive symptoms (Corcoran et al., 2003). A recent cross-sectional study of a cohort of clinical schizophrenia high-risk patients showed that cortisol secretion was related to suspiciousness, anxiety and impaired stress tolerance and depression (Corcoran et al., 2012).

Another potential pathway is the impact of childhood maltreatment on neural structure and function (McCrory et al., 2011). Some evidence shows that children and adults who have experienced adversity have smaller intracranial and cerebral volume, smaller volume of corpus callosum (CC) and larger lateral ventricular volume compared to non-maltreated children or adults (De Bellis et al., 1999). Other studies show a greater amygdala volume in late-adopted previously institutionalized children (Mehta et al., 2009; Tottenham et al., 2010) and a relatively clear pattern of normal hippocampal volume during childhood (Mehta et al., 2009), which contrasts with the finding of reduced hippocampal volume seen in adults with histories of abuse (Woon & Hedges, 2008). Previous studies have shown a mainly left-sided smaller hippocampal volume in patients with first-episode psychosis as well (Steen et al., 2006; Velakoulis et al., 2006) and this may be explained by stress-related processes in the brain, as measured by cortisol hyper-secretion (Mondelli et al., 2010b).

Structural findings are mixed for the prefrontal cortex (PFC) in maltreated children, but there is reportedly a pattern of decreased PFC volume among adults with childhood histories of maltreatment (De Bellis et al., 1999; 2002). However, a recent finding highlights that physically abused children show a significantly smaller brain volume in the orbitofrontal cortex (OFC) correlated with poor social functioning (Hanson et al., 2010). Moreover, studies of adults using fMRI suggest that the experience of maltreatment may be associated with hyperactivity of the amygdala in response to negative facial affect; such an effect has also been reported in children who have experienced early institutionalisation (McCrory et al., 2011). Studies of maltreated children that have examined response inhibition have observed increased activity in the

anterior cingulate cortex (ACC; McCrory et al., 2011). Event-related potential (ERP) studies have found increased responses to angry faces in prefrontal regions consistent with increased attentional monitoring for social threat. It has been hypothesized that a brain system including the insula and the ACC may function abnormally also in schizophrenia (Gradin et al., 2013; Palaniyappan & Liddle, 2012).

The role of demographic factors in the association between childhood adversity and psychosis

The association between childhood adversity and psychosis by specific demographic factors, such as gender or ethnicity, has not been systematically explored (Morgan & Fisher, 2007; Morgan et al., 2010). Gender differences in rates of internalizing disorders, particularly depression, are well documented (Gershon et al., 2008). One potential hypothesis proposes that higher rates of depression in females compared to males may be partially attributable to gender differences in the effects of childhood sexual abuse (Cutler & Nolen-Hoeksema, 1991). This hypothesis has been supported by findings in the epidemiology of posttraumatic stress disorder (PTSD) that consistently reported a higher risk of this disorder in women (Breslau et al., 1997; Kessler et al., 1995; Stein et al., 2000; Walker et al., 2004). Explanations reviewed within a psychobiological model of PTSD suggest that women's higher PTSD risk may be due to the type of trauma they experience, with a more pronounced effect for interpersonal traumas such as physical assault and rape (Breslau et al., 1999; Norris, 1992), as well as their stronger perceptions of threat and loss of control (Olff et al., 2007).

The few studies conducted in psychosis samples so far evidenced that the specific link between sexual abuse and psychosis is moderated by sex, being stronger for females (Bebbington et al., 2011; Fisher et al., 2009). This is consistent with evidence from Myin-Germeys et al. (2004) that psychosis in females is a more socially reactive condition than in males, with women being more vulnerable than men to the effects of daily life stress. Several studies in the

general population have also demonstrated that women are exposed to more life-events and daily stressors compared with men (Almeida & Kessler, 1998; Turner & Avison, 1989). Therefore, a higher level of stress reactivity may also be the result of higher levels of exposure to stressors in women compared with men (Myin-Germeys et al., 2003) which, in turn, increase the risk to develop psychosis in this group.

The association between childhood adversity and psychosis seems to also be moderated by ethnic group (Morgan & Fearon, 2007; Morgan et al., 2007). Specifically, separation from a parent due to family breakdown in childhood has been found to be more common in African-Caribbean and Black African psychosis cases in the UK compared to the White British cases (Mallet et al., 2002; Morgan et al., 2007; Morgan et al., 2008). The higher prevalence of separations in the Black population might be an indicator of the relative disadvantage experienced by this population in the UK and supports the hypothesis of a socio-developmental pathway to psychosis (Morgan et al., 2010). Through cumulative disadvantage processes, people who face more adversity in childhood are more likely to encounter stressors in adulthood; the accumulation of stress over the life course is often associated with poor outcomes in a number of domains (e.g. education, health, housing, relationships, etc.), further creating a vicious cycle of poverty and exclusion (Pantazis et al., 2006).

Similarly, Warner and Hayward (2006) suggest that the disparities between black and white adults in the levels of support and strain in their social relationships have their origins, in part, in differential exposure to childhood social conditions. Racial segregation and discrimination early in life expose black children to poverty and more stressful environments that may promote social isolation and conflict, undermine relationship quality, and limit resources offered by social support later in life (Massey, 2004; Warner & Hayward 2006; Williams & Sternthal, 2010). Therefore, it may be that there is a vicious cycle in which chronic underlying socio-economic adversity and discrimination affects family life in such a way as to increase the risk of family breakdown, which further impacts

on socio-economic resources and increases the risk of a range of mental health outcomes, including psychosis (Morgan et al., 2007).

Childhood adversity, diagnosis, dimensions and symptoms of psychosis

Recent studies have shown evidence of specificity between childhood adverse events and manifestations of psychotic disorders (Bendall et al., 2013). For example, high rates of childhood adversity have been reported in patients with schizophrenia (Friedman et al., 2002; Hlastala & McClellan, 2005; Morgan et al., 2007; Ross et al., 1994). However, Bebbington et al. (2004) and Shevlin et al. (2007a) reported that their associations between adverse experiences and psychosis were attenuated by depressed mood, suggesting that childhood adversity might be also be prevalent (if not even more so) amongst those with an affective psychosis diagnosis. Affective dysregulation following childhood adversity has been increasingly highlighted as a mechanism through which psychosis develops (Garety et al., 2001; van Winkel et al., 2013). 'The affective pathway to psychosis' (Myin-Germeys & van Os, 2007) hypothesis postulates that childhood trauma may initially give rise to affective symptoms, with an elevated emotional reactivity to daily life stress and only later leading to psychotic symptoms.

There is now good evidence that specific ancillary symptoms of psychosis might operate as mediators between external experience and psychotic symptoms; for example, affective symptoms frequently precede the onset of psychosis (Bebbington, 2015). Childhood trauma increases the likelihood of a specific admixture of affective, anxiety and psychotic symptoms cutting across traditional diagnostic boundaries, and this admixture may already be present in the earliest stages of psychopathology (van Nierop et al., 2015). Previous studies show that clustering of hallucinations and delusional ideation is associated to the presence of affective dysregulation (Smeets et al., 2012).

Therefore, the phenotypic expression of psychosis may not be limited to people who have received a diagnosis. A continuum hypothesis, recognising the

psychosis phenotype as a continuous distribution of symptoms with individuals differing quantitatively rather than qualitatively, continues to be demonstrated (Johns & van Os, 2001; Murphy et al., 2012). It is now widely accepted that psychotic symptoms partition into several symptom dimensions. Symptoms and symptom dimensional models of psychosis are now frequently investigated in the literature and have also become useful in therapeutic settings (Allardyce et al., 2007). The existence of five specific affective and non-affective psychosis dimensions (positive symptoms, negative symptoms, disorganisation, mania, and depression) has received increasing support from evidence suggesting that genetic and environmental risks are shared among affective and non-affective psychotic disorders (Reininghaus et al., 2013) and that the predictive validity of psychopathological dimensions in the functional psychoses is higher than that of traditional diagnostic categories (van Os et al., 1996). A recent study found associations between childhood parental separation, sexual and physical abuse with the positive dimension; while being taken into care was associated with the excited dimension (Ajnakina et al., 2015), suggesting that distinct pathways may be involved in the CA-psychosis association.

Furthermore, Bentall et al. (2014) postulates a certain degree of specificity also between specific types of adversity and development of psychotic symptoms. For example, abnormal family communication and experience of maltreatment in childhood might lead to thought disorder in psychotic offspring (Harrow & Quinlan, 1985; Sass et al., 1984; Singer & Wynne, 1965; Tompson et al., 2007) as result of a dysregulation of the HPA axis and consequent alterations in the dopaminergic and serotoninergic systems (Sheree et al., 2011).

Childhood sexual abuse may be a particularly potent risk factor for hallucinations (Hammersley et al., 2003; Read & Argyle, 1999; Shevlin et al., 2007b) as consequences of dissociative processes that may be trauma-related (Longden et al., 2011; Moskowitz & Corstens, 2007; Perona-Garcelan et al., 2012; Varese et al., 2011, 2012b). Hallucinations, especially in the auditory verbal form, may be a consequence of a failure of the cognitive processes involved in

discriminating between internal and external perceptions, processes known as source monitoring or self-monitoring (Frith, 1992). It has also been hypothesized that, at the neurocognitive level, these deficits are associated with impaired connectivity between frontal, speech-generating areas of the brain and the auditory cortex (Ford et al., 2007; Whitford et al., 2011).

Additionally, chronic victimization and discrimination, being brought up in a children's home and childhood neglect, showed associations with paranoid symptoms (Bentall et al., 2012; Janssen et al., 2003; Mirowsky & Ross, 1983) and interpreted as evidence of inadequate early attachment (Sitko et al., 2014).

Childhood adversity therefore may influence psychosis at a level of diagnosed psychiatric disorder, symptom dimensions as well as at the specific symptom level.

Childhood adversity and course of illness

The literature on the effects of childhood adversity on the course of mental illnesses has been mainly focused on patients with non-psychotic disorders. In fact, several studies have shown that childhood adversity may predict an unfavourable course of depression and treatment outcome. Compared with individuals without a history of childhood adversity, those with such a history of adversity have an increased risk for meeting criteria for a depressive episode at any point in their life (Ford & Erlinger, 2004; Kessler, 1997), cognitive impairment (Beck, 2008) and elevated inflammation levels (Danese et al., 2007; 2008) associated with heightened stress sensitivity (Hammen et al., 2000), which might predispose them to an unfavourable course of illness and treatment outcome (Lanquillon et al., 2000). Indeed, a recent meta-analysis examining the relationship between childhood maltreatment and clinically relevant measures of depression, such as course of illness and treatment outcome, reported that maltreated individuals were twice as likely as those without such a history to develop both recurrent and persistent depressive episodes (Nanni et al., 2012). Findings from clinical trials were consistent with the epidemiological

observations showing that, compared with depressed individuals without a history of childhood maltreatment, depressed and maltreated patients appeared less responsive to pharmacological, psychological or combined treatment, and had a greater risk of recurrent and persistent depressive episodes (Nanni et al., 2012).

Moreover, in patients with bipolar disorder, childhood adversity has been associated with earlier age of onset, worse clinical evolution, more suicide attempts, increased number of comorbid disorders including lifetime substance abuse, and higher prevalence of a faster cycling pattern (Garno et al., 2005; Dilsaver et al., 2007; Leverich et al., 2002). However, in another study authors did not find a connection between any type of adversity and earlier diagnosis of bipolar disorder that could be related to the age at which the diagnosis was made (Alvarez et al., 2011). Leverich et al. (2002) showed a lag of 13 years between the onset of symptoms and diagnosis in a group of patients who had been severely traumatized in childhood, compared with 8 years in those who had not. Alvarez et al. (2011) found significant differences in the number of admissions in the previous 2 years in bipolar patients with a history of psychological abuse in childhood but not with physical or sexual abuse.

Maguire et al. (2008) reported that, in a bipolar disorder sample, childhood adversity predicted the frequency of hospital admissions, quality of life, and inter-episode depressive symptoms. Interpersonal difficulties, but not alcohol dependence, appeared to play an important role in mediating these adverse effects. Interestingly, a study reported that at 6-month follow-up, persons whose first exposure to adversity occurred after age 16 were the most symptomatic, but at 24-month follow-up, those with childhood adversity had the poorest outcome in terms of number of episodes, general distress, and depressive symptoms (Neria et al., 2005). Moreover, a high frequency of positive symptoms, especially auditory hallucinations, has been found in patients with bipolar disorder and a history of childhood abuse (Hammersley et al., 2003).

Surprisingly, the number of studies investigating the effect of childhood adversity on clinical and social outcomes in psychosis is still small and they have usually been conducted in samples of chronic patients, leading to potential selection biases due to the effect of long-lasting illness and/or treatment (Conus et al., 2010). In the next paragraphs, I will summarise the findings on the association between childhood adversity and clinical and social outcomes in psychosis to date. I will first present the results of a systematic review and meta-analysis of the impact of childhood adversity on the course of psychotic symptoms, which I carried out with the help of my supervisors. A literature review on the association between childhood adversity and functional course of psychosis will also be provided.

Systematic review and meta-analysis of the impact of childhood adversity on the persistence of clinical psychotic symptoms

This section represents an extract from a broader systematic review and meta-analysis examining the impact of childhood adversity on persistence of subclinical and clinically relevant psychotic symptoms, focusing on trajectories of change in psychosis-like experiences (PLEs) and psychotic symptoms over time. In the original work, in order to describe symptom trajectories I focused on studies utilising general population samples, individuals at Ultra High Risk (UHR) of psychosis, patients with first-episode psychosis (FEP) and patients with chronic psychosis (see Appendix II).

Recent studies indicate that environmental risk factors are associated with persistence of subclinical psychotic experiences in some individuals (Cougnard et al., 2007), and that greater levels of persistence in turn predict greater risk of transition to psychotic disorders (Dominguez et al., 2011). In fact, a number of early life characteristics and markers of childhood emotional and behavioural development are associated with trajectories of these psychotic-like experiences (PLEs) during adolescence. Children with persistent PLEs have been

shown to be more likely to come from adverse backgrounds and have disturbed childhood development compared to those with more transient PLEs (Thapar et al., 2012). A potential causal mechanism may reside in neurodevelopmental abnormalities and permanent damage in the stress regulation system due to exposure to childhood adversity (Cougnard et al., 2007). The persistence of exposure to stressors and the chronicity of heightened glucocorticoid release, can induce permanent changes in the HPA axis and, through this, affect the dopamine system (Walker & Diforio, 1997), which has also been associated with development and persistence of psychosis (Mondelli et al., 2015).

Nevertheless, only a few studies have focused on the course of full-blown psychotic disorder and, in keeping with previous studies on the other patient populations presented above, some studies have demonstrated that victims of childhood adversity have poorer outcomes characterised by a higher number of suicide attempts, earlier onset of psychosis, and poor medication adherence (Alvarez et al., 2011; Garno et al., 2005; Lecomte et al., 2008). However, other studies did not show significant evidence of the impact of childhood adversity on the course of psychotic symptoms (Cohen et al., 2012; Davidson et al., 2009; Gil et al., 2009; Kim et al., 2006; Newman et al., 2010).

Therefore, despite evidence suggesting that childhood adversity is related to heightened symptom levels (Heins et al., 2011, Ross et al., 1994), it is still not clear what the impact is on the evolution of psychotic symptoms over time. Therefore, this section presents a systematic review of the available empirical literature, examining the impact of childhood adversity on persistence of clinically-relevant psychotic symptoms, focusing on the course of psychotic symptoms after illness onset over time.

Methods

Literature search and selection criteria

I followed the PRISMA statement guidelines for systematic review and meta-analysis in this study (Moher et al., 2009). A systematic database search from 1st

January 1956 up to 30th November 2014 was performed on Medline (PubMed), Embase and PsychINFO databases using search terms related to: (1) childhood adversity, (2) psychosis and (3) course of clinical psychotic symptoms, using the Boolean operator "and" (full list provided in Appendix III).

Studies were included if (a) they assessed adverse events in childhood, (b) follow-up yielded outcome data (in the clinical psychotic symptom domain), and (c) they were published in English in peer-reviewed journals. Studies were excluded if (a) they assessed adverse events that occurred in adulthood, (b) the study involved a clinical sample that included organic etiology of psychosis or substance-induced psychosis, with no separate data provided, and (c) clinical outcome was not explicitly defined. Childhood was defined as aged 18 years or below. FEP was defined as patients who were: making their first treatment contact for a psychotic disorder (non-affective and affective psychoses) OR in their first admission for a psychotic disorder OR in their first episode of psychosis. Adversity included all forms of childhood abuse and neglect, parental death or separation, bullying by peers and being taken into care. Additional studies were identified by hand searching the bibliographies of each article found. Where the same study was reported in more than one publication, the dataset was only included once. Only studies with sufficient statistical information for the computation of effects comparable to other reported studies were included. Each study was assessed using a quality assessment tool (see Appendix III) adapted from Beards et al. (2013). A cutoff score of at least 11 out of 14 (over 70%) was chosen to define the more "methodologically robust" studies, based on criteria such as sample selection bias, measurement of exposure to childhood adversity, measurement of psychotic symptoms, and assessment of confounding.

Statistical Analyses

All analyses were carried out using the meta-analysis commands of Stata 11 (StataCorp, 2009). I chose odds ratios (ORs) as the main outcome metric. When

not reported in the primary studies, ORs and their associated standard errors were estimated from available descriptive statistics (i.e., frequencies) using standard computational techniques for dichotomous data.

To examine the global association between adverse childhood events and persistence of psychotic symptoms, a meta-analysis was carried out on the effects extracted from studies providing a summary measure of exposure to childhood adversity. When this information was not available, i.e. in the absence of a summary measure of childhood adversity or studies reporting multiple effects for the associations between adverse events and specific psychotic symptoms, reports were excluded from the meta-analysis to avoid bias stemming from the violation of statistical independence. Standardized effect sizes were meta-analyzed using random effects models. Heterogeneity between studies was assessed with the Q test (DerSimonian & Laird, 1986). The I^2 statistic was calculated to express the proportion of variation between studies that was due to heterogeneity (Higgins et al., 2003). The results are displayed using a forest plot.

Further exploration of heterogeneity was carried out using meta-regression analyses for testing effects of the following potential moderator variables: inclusion of adjusted or unadjusted effect sizes, year of publication, quality score, and length of follow-up. Egger's test of publication bias was used to assess whether there was a tendency for selective publication of studies based on the nature and direction of the results (Egger et al., 1997). A significance level of $p<0.05$ was used for the random effects model, homogeneity, publication bias and meta-regression analyses.

Results

The original search yielded a total of 2824 studies (see Appendix II). On the basis of title and abstract, a total of 243 studies were considered potentially relevant and the full text of each was assessed manually. For the purpose of this chapter, I have only included studies conducted on patients with a full-blown psychotic

disorder. A summary of the eight eligible studies and their empirical findings relating to the association between childhood adversity and persistence of clinically-relevant psychotic symptoms can be seen in Table 1.1. Of these, only 3 studies scored above the cut-off of 11 or more [70% or over] and thus can be considered to have a reasonable level of methodological quality.

Childhood adversity and persistence of symptoms in patients with clinically-relevant psychotic disorders

A total of eight studies were conducted on patients with a full-blown psychotic disorder. Four studies investigated the association between childhood adversity and course of psychotic symptoms in first-episode psychosis samples with mixed findings. Álvarez-Jiménez et al. (2011) found that the loss of one or both parents was associated with a four-fold increased risk of having more than one psychotic episode over a 7.5-year follow-up period. However, two studies (Conus et al., 2010; Greenfield et al., 1994) observed no significant differences between sexually and/or physically abused and non-abused psychosis patients in terms of symptomatic remission (OR=0.88, p=0.150) or recovery over 18 months following first admission. Similarly, Uçok and Bickmaz (2007), in their 6 months follow-up study, reported no correlation between sexual or physical abuse and severity of positive or negative symptoms but significant correlations for emotional abuse and emotional and physical neglect. Studies on FEP focused on different types of adversity and psychosis outcomes which makes difficult to compare their results.

A total of four studies focused on non-first-episode psychosis cases. In the study by Davidson et al. (2009), 55% of participants from community mental health services in Northern Ireland reported a history of childhood adversity. Although the authors reported no statistically significant differences between those with and without a history of childhood adversity in terms of the course of psychotic symptoms over time, patients who reported childhood abuse and/or neglect had higher positive and negative symptom scores at all the three assessments (baseline, 9 and 18 months) compared to patients who did not.

Similarly, in the GROUP study sample (van Dam et al., 2014), individuals with childhood abuse or neglect reported higher levels of symptoms at both baseline and 3-year follow-up compared to individuals without such reports, indicating that heightened symptom levels were present over time. Interestingly, these results were consistent in unaffected siblings and controls, with those reporting high trauma during childhood also having higher schizotypy levels at both baseline and follow-up. However, the association between trauma and developmental course of psychotic symptoms and schizotypy did not reach statistical significance. Similar findings come from shorter follow-up studies, with patients reporting physical or sexual abuse having higher levels of positive symptoms over 4 months and more frequent relapses over one year than patients not reporting abuse histories (Goff et al., 1991; Lysaker et al., 2005). However, the numbers of patients in these two studies was relatively small (<100 in each study) and no other types of adversity were considered so the generalisability of these findings is limited.

Table 1.1 Studies included in the review which explore the association between childhood adversity and persistence of psychotic symptoms spilt into first-episode and non first-episode psychosis patient samples (Taken from Trotta el al., 2015a).

Authors/study	N[a]	Follow-up period[b]	Type of childhood adversity	Measure of childhood adversity	Outcome measure and definition	Main findings	Quality score
First-episode psychosis studies							
Alvarez-Jimenez et al., 2011 (Australia)	At baseline: 413 At follow up: 274 Prevalence of parental loss (n): 15% (41)	7.5 years	Parental loss	Information obtained from the patient, family members, members of the specialist treatment team or general practitioner and examination of psychiatric/research medical records	Number of psychotic episodes WHO Life Chart Schedule (LCS) (World Health Organization, 1992b)	Loss of one or both parents increased the risk of having more than one psychotic episode fourfold (Adj OR=5.25; 95% CI: 1.03–26.68, p=0.045)	11
Conus et al., 2010 (Australia)	At baseline: 658 At follow-up: 230 Separation of parents (42.1%, n=277), physical abuse (26.0%, n=171), sexual abuse (16.0%, n=105). 34% reporting sexual or physical abuse (SPA)	18 months	Sexual and/or physical abuse (SPA).	Early Psychosis File Questionnaire (EPFQ; Conus et al., 2007).	Severity of illness Clinical Global Impressions-Severity of Illness Scale (CGI-S; Guy, 1976).	SPA was not related to either symptomatic (OR=0.88, 95% CI: 0.75–1.05; p=0.150) remission at discharge.	13

Authors/study	N[a]	Follow-up period[b]	Type of childhood adversity	Measure of childhood adversity	Outcome measure and definition	Main findings	Quality score
Greenfield et al., 1994 (USA)	At baseline: 71 At follow-up: 38 Prevalence of physical abuse (n=9, 23.7%); sexual abuse (n=3, 7.9%), physical and sexual abuse (n=8, 21.1%).	18 months	Childhood sexual and physical abuse.	Life Experiences Questionnaire (LEQ; Bryer et al., 1987).	Psychotic symptoms Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962); Clinical Global Impression Scale (CGI; Guy, 1976).	No significant differences in recovery rates were observed between abused and non-abused subgroups.	7
Ucok & Bickmaz, 2007 (Turkey)	At baseline: 75 At follow-up: 57	6 months	Childhood sexual, physical, emotional abuse and physical and emotional neglect.	Childhood Abuse Questionnaire (CAQ; Sar et al., 1999). Childhood Trauma Questionnaire's short version (CTQ; Bernstein and Fink, 1998).	Psychotic symptoms Brief Psychiatric Research Scale (BPRS; Ventura et al., 1993) Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984); Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983)	Significant association between emotional abuse and total score for positive symptoms (r=0.278, p=0.04), visual hallucinations (r=0.289, p=0.03), delusions of reference (r=0.385, p=0.005) and mind reading (r=0.381, p=0.006). Patients who reported childhood emotional neglect (CEN) had higher psychiatric symptoms (69.6, SD=15.9 vs. 60.3, SD=13, Z=-2, p=0.04), delusions of reference scores. Physical neglect was linked to the severity of visual and tactile hallucinations (Z=2.1, p=0.03)	9

Authors/study	N[a]	Follow-up period[b]	Type of childhood adversity	Measure of childhood adversity	Outcome measure and definition	Main findings	Quality score
Non First-Episode Psychosis studies							
Davidson et al., 2009 Northern Irish study (Northern Ireland)	At baseline: 41 At follow-up: 31 Prevalence of childhood trauma (n): 55% (17)	18 months	Emotional, physical and sexual abuse, emotional and physical neglect	Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998)	Positive and negative psychotic symptoms The revised Manchester Scale, KGVM (Krawiecka Goldberg Vaughan–Modified) Symptom Scale (Krawiecka, Goldberg, & Vaughan, 1977) Version 6.2 (Lancashire, 1998)	No differences between the no childhood trauma (n = 14) and childhood trauma groups on KGVM score over 18 months ($F(1, 27)=2.31$, $p>0.05$)	9
Goff et al., 1991 Erich Lindemann Mental Health Center, Massachusetts General Hospital. (Massachusetts, USA)	At baseline: 72 At follow-up: 62 Prevalence of childhood abuse (n): 37.5% (27)	1 year	Physical and sexual abuse	Life Experiences Questionnaire (Bryer et al., 1987)	Delusions, hallucinations, and thought disorder. Structured Clinical Interview for DSMIII- R (SCID; Spitzer et al., 1987) Structured Clinical Interview for DSM-III R Dissociative Disorders (SCID-D; Steinberg et al., 1990). Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962).	Patients reporting childhood abuse relapsed more frequently than patients not reporting abuse histories ($M=1.7$; $SD: 2.3$; $p<0.05$).	12
Lysaker et al., 2005 VA Medical Center (Indiana, USA)	At baseline: 65 At follow-up: 43 Prevalence of childhood abuse (n): 28% (18)	4 months	Sexual abuse	The Childhood Experiences Questionnaire (CEQ; Levitan et al., 1998)	Positive symptoms and emotional discomfort symptoms. The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987)	The abuse group had overall higher positive component scores ($F[1,41]= 4.12$; $p<0.05$). An interaction between group and time was noted at the trend level ($F[7,41]= 1.92$; $p=0.07$).	7

Authors/study	N[a]	Follow-up period[b]	Type of childhood adversity	Measure of childhood adversity	Outcome measure and definition	Main findings	Quality score
van Dam et al., 2014 GROUP study (The Netherlands and Belgium)	At baseline: 1119 At follow up: 633 Prevalence of childhood adversity (n): 44% (336)	3 years	Emotional, physical and sexual abuse, emotional and physical neglect.	Dutch version of the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003; Thombs et al., 2009)	Positive and negative psychotic symptoms The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987)	Total trauma associated with more severe positive and negative symptoms: Baseline Positive symptoms, mean (SD): Low trauma 1.65 (0.67) vs High trauma 2.01 (0.91); Follow-up, mean (SD): Low trauma 1.47 (0.59) vs High trauma 1.70 (0.69). Baseline Negative symptoms, mean (SD): Low trauma 1.81 (0.80) vs High trauma 2.01 (0.94); Follow-up, mean (SD): Low trauma 1.60 (0.64) vs High trauma 1.72 (0.79).	12

Adj., adjusted; CI, confidence interval; HR, hazard ratio; M, mean; OR, odds ratio; SD, standard deviation; SE, standard error.

Meta-analysis

Additionally, I carried out a meta-analysis of a subset of 4 studies in which the ORs between adverse childhood events and persistence of clinically-relevant psychotic symptoms had been reported (Figure 1.1). The meta-analysis for clinical population studies yielded a weighted OR of 1.55 (95% CI 0.32-2.77), which suggests that individuals exposed to childhood adversity are approximately 1.5 times more likely to report persistence of psychotic symptoms than those who reported no history of exposure to childhood adversity. However, as the confidence interval crosses 1, there is no statistical difference between those exposed to childhood adversity compared to those unexposed in terms of persistence of symptoms.

Interestingly, in the original meta-analysis, the OR reported from the general population studies on persistence of PLEs (OR of 1.76; 95% CI 1.19-2.32, $p<0.001$) was similar to that obtained from the clinical samples, indicating a significant association between childhood adversity and persistence of psychotic phenomena even before illness onset. There was no significant heterogeneity for clinical population studies ($I^2=0\%$, $p=0.407$). In meta-regression analyses, there were no effects of inclusion of adjusted or unadjusted effect sizes, year of publication, quality score, or length of follow up.

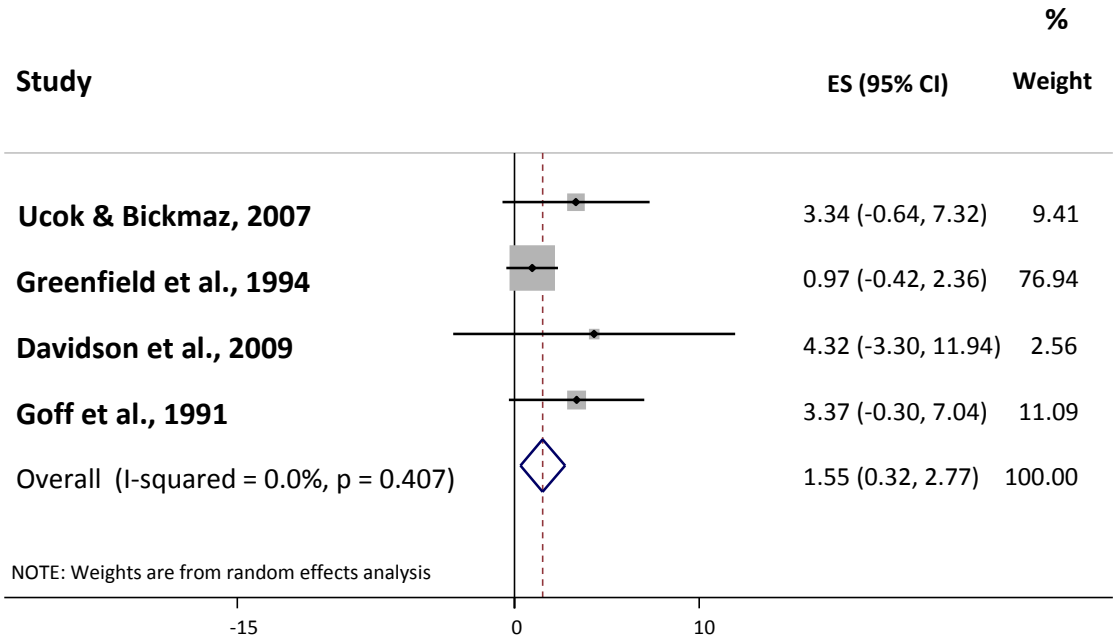

Figure 1.1 Forest plot for the meta-analysis examining the overall association between childhood adversity and persistence of psychotic symptoms (Taken from Trotta el al., 2015a).

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Discussion

The goal of this review was to combine results from existing studies exploring the association between childhood adversity and course of psychotic symptoms, which is novel for the literature. There were two main findings: (a) the literature on childhood adversity and persistence of psychotic symptoms in clinical samples is surprisingly small (only 8 studies spread over 23 years); (b) most studies suggest that childhood adversity impacts on the course of clinical psychotic symptoms, with my meta-analysis suggesting around 1.5 increased odds of persistence of psychotic symptoms in those reporting childhood adversity compared to those who did not, though the association could not considered significant as the confidence interval crosses 1. Therefore, the findings of this review tentatively suggest that exposure to childhood adversity may lead to a worse clinical course of psychotic symptoms though, due to small number of

studies included, this effect has not been statistically confirmed by the meta-analysis.

Studies focusing on patients with clinically relevant psychotic disorders reported that exposure to childhood adversity was associated with higher risk of relapses (Alvarez-Jimenez et al. 2011; Goff et al., 1991), and higher levels of symptoms over time (Lysaker et al., 2005; Uçok & Bickmaz, 2007; Van Dam et al., 2014). However, findings on clinical samples are still not consistent and some studies did not confirm the effect of childhood adversity on symptom course (e.g., Davidson et al., 2009; Conus et al., 2010; Greenfield et al., 1994).

How could childhood adversity impact on the clinical course of psychosis?

The childhood trauma literature, suggests that adversities are damaging if they are overwhelming and persistent. This is supported by the findings of morphological and functional brain alterations found in exposed populations (Chugani et al., 2001; Thomas & De Bellis, 2004; Teicher et al., 2012, 2013; Kelly et al., 2013). Removal from traumatising environments improves the later outcomes of emotional, cognitive and psychiatric difficulties (Perry, 2002; Teicher et al., 2003) and thus remaining in such an adverse environment may prolong symptoms.

Dysfunctional emotional processing has been found to be a mediator between childhood adversities and psychotic symptoms (Kramer et al., 2012). Emotional dysregulation, in fact, might influence the appraisals of psychosis symptoms, such as voice controllability, delusional preoccupation, and conviction, and might lead to poorer outcomes in terms of positive symptoms, relapse and readmissions over time (Bebbington & Kuipers, 1994).

Higher levels of expressed emotions in the family (EE), including emotional over-involvement and critical comments, have been found to be associated with a higher number of rehospitalisation and relapses over 20 years and intensification of the positive syndrome in both the short-term and long-term course of the illness (Cechnicki et al., 2013)

Methodological issues

The results of this review should be interpreted in the context of the strengths and limitations of the studies included. A major strength is that all 8 studies included in this review used a prospective design. This design allows us to tentatively make causal inferences regarding the association between childhood adversity and course of psychotic symptoms compared to cross-sectional studies, at least in terms of the temporal ordering of exposure and outcome. Another important strength of the studies in this literature review was that data on clinical psychotic symptoms was also available at different time-points, allowing inferences to be made on potential trajectories in the prodromal phase as well as after the illness onset. Furthermore, trajectory-based analyses are more robust to occasional misreporting or temporary fluctuations in a condition compared to data collection at a single time-point (Willett & Sayer, 1994; Wang & Bodner, 2007). Finally, the prevalence rate of childhood adversity, within the studies reviewed here varied between 8.5% and 69.6% in clinical samples, depending on the type of childhood adversity studied. This is similar to rates found in previous reviews of adversity and psychosis onset (Read et al., 2005; Varese et al. 2012).

However, there are a number of methodological limitations to the studies included in this review. A significant one is the variability in definitions and study parameters making comparisons between studies difficult and limiting the generalisability of findings. Differences in childhood adversity measurement may account for some of the variations in findings. Instruments to assess childhood adversity generally fall into two categories: checklist or semi-structured interview. Of the studies reviewed, 6 used checklists and 2 studies used semi-structured interview. Thus differing rates of experiences may have been captured by the different assessment tools. Additionally, the majority of studies included in this review relied on retrospective self-reports of childhood adversity. Self-report of childhood trauma has been criticised because of the susceptibility to memory deficiencies and imagining events that are core aspects of psychosis

(Howard, 1993; Lysaker et al., 2005; Young et al., 2001) which might lead to over-reporting of adversity exposure. However, it has been shown that reports of early adversity by psychotic patients appear reliable over time and between assessment methods (Fisher et al., 2011).

The assessment of outcome variables was also not uniform across the studies and heterogeneity was apparent for assessment of clinical psychotic symptoms. For example, Conus et al. (2010) and Greenfield et al. (1994) studies used a 7-point scale to rate the overall severity of the patients' illness (CGI-S; Guy, 1976) while Ucok & Bickmaz (2007), Goff et al. (1991) and Lysaker et al. (2005) used more in depth interviews to assess positive and negative symptoms of psychosis, e.g. Structured Clinical Interview for DSM (SCID Spitzer et al., 1987) or Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The heterogeneity of outcome definitions as well as the different types and severity of childhood adversity included reduce the comparability and sample size for each variable, limiting the validity and relevance of conclusions.

Moreover, causal interpretations in clinical studies are limited by the small number of first-episode and non-first-episode psychosis samples available and by the lower methodological quality of studies. It is clear that more methodologically robust studies based on clinical samples are needed, which utilize appropriate outcome measures and objective ratings of the impact of childhood adversity. Finally, adjustment for potential confounders was inconsistent. Where adjustments were made, the majority controlled for age, gender, and ethnicity, with some controlling for a wider range of factors, such as substance use or psychotic symptoms at baseline, and education. No study adjusted for adversity occurring in adulthood which has also been associated with the onset and course of psychosis (Beards et al., 2013).

Childhood adversity and social course of psychosis

Previous studies have shown that patients with psychosis who reported a history of childhood adversity had higher rates of avoidance and discomfort with

closeness (Couture et al., 2007), and fewer of the psychological resources necessary for sustaining intimacy (Lysaker et al., 2005) compared to those without such a history. Similar findings come from studies on adults with PTSD (Mazza et al., 2012; Nazarov et al., 2014) that highlight an association between emotional distress and significant deficits in metacognition, namely the capacity of thinking about the thoughts and feelings of others (Lysaker et al., 2015). Metacognition is affected by parental communication and attachment (Meins et al., 2002); interpersonal trauma in childhood may disrupt the attainment of social relationship skills and thus impair the ability to initiate and maintain satisfying relationships in adulthood (Klohnen & Bera, 1998; Swanson & Mallinckrodt, 2001).

Consistent with attachment theory, it has been shown that early disruption of attachment in childhood (for example through an attachment figure abusing a child) leads to the development and maintenance of interpersonal difficulties over the life-span (Berry et al., 2007). Therefore, psychosis patients with a history of adversity in childhood might be expected to be less likely to be in a relationship at follow-up. Additionally, longitudinal attachment studies suggest that social functioning difficulties such as social isolation, communication abnormalities, and disturbed peer relationships predispose individuals to the development of psychosis (Mason et al., 2004). Specifically, sexual abuse (Lysaker et al., 2011b) and early institutional deprivation (Colvert et al., 2008) have been reported to lead to a decreased capacity to recognise one's own emotions and the emotions of others, a key aspect of social cognition that has been shown to be specifically linked to deficits in social functioning (Bora et al., 2006, Lysaker et al., 2011a; Pinkham et al., 2003). Deficits in the capacity to "think about thinking" may limit abilities to form a coherent image of oneself as functioning within a social context and may lead in turn to incapacity to resolve the conflicts and misunderstandings arising in daily life (Lysaker et al., 2011a). Such incapacity to fine-tune to others in complex

situations may contribute to poorer social and vocational adjustment in adulthood.

In terms of social and vocational functioning, the literature on the impact of childhood adversity on these types of psychosis outcomes is also very limited. Previous studies have reported that childhood adversity is linked with a higher rate of unemployment, increased number of hospital admissions and service costs, and these detrimental outcomes are maintained over time (Davidson et al., 2009; Alvarez et al., 2011). Specifically, sexual abuse in childhood has been associated with poorer psychosocial functioning in adults with schizophrenia (Gil et al., 2009; Lysaker et al., 2001; 2004). Extending these cross-sectional findings, Lysaker et al. (2005) also showed that poorer social functioning levels, together with higher symptoms, were maintained over time amongst those with a history of childhood sexual abuse.

As for clinical outcomes, in first-episode studies differentially defined social outcomes were reported across studies. Álvarez-Jiménez et al. (2012) assessed full functional recovery throughout a 7.5 year follow-up period using a semi-structured interview (WHO Life Chart Schedule [LCS]; World Health Organization, 1992b), selected items from the Quality of Life Scale (QLS; Heinrichs et al., 1984) and Social and Occupational Functioning Assessment Scale (SOFAS; Goldman et al., 1992). In line with a previously published study (Robinson et al., 2004), Full Functional Recovery (FFR) was defined by the authors as comprising four components: appropriate interpersonal relationships with people outside the family; adequate vocational functioning defined as paid employment, attending school or, if a home-maker, performing that role efficiently and adequate accomplishment, defined as success in fulfilling the particular role that the person had chosen to attempt. The fourth component of FFR was regular participation in basic living tasks. In Conus et al. (2010), functional remission was defined as employment based on Modified Vocation Code Index (MVCI; Tohen et al., 2000) (paid or unpaid full- or part-time employment, being an active student in school or university, head of household

with employed partner, or full or part-time volunteer) and independent living based on Modified Location Code Index (MLCI; Tohen et al., 2000) (head of household; living alone, with partner, or with peers; and living with family with minimal supervision) at discharge.

The variety of outcomes measured is expressed by the differences in results reported on the association between childhood adversity and psychosis outcome between studies. Álvarez-Jiménez et al. (2012) found that the loss of one or both parents increased the risk of having worse social/vocational recovery over a 7.5-year follow-up period (OR=2.25, p=0.113). Conus et al. (2010) found that patients who had a history of sexual and/or physical abuse (SPA) was not associated with functional remission. Greenfield et al. (1994) observed that patients reporting childhood abuse tended to have a longer hospital stay (Z=-1.9, p=0.06). Only emotional abuse and physical and emotional neglect were associated with functional impairment in patients with schizophrenia. The Gil et al. (2009) study found that specific types of abuse and neglect, such as physical neglect and emotional abuse and neglect, influenced disability, and the most robust association was with physical neglect.

Therefore, it can be concluded that, to date, only a few studies have focused on social outcomes of psychosis amongst psychosis patients reporting childhood adversity and their results are quite contradictory. Moreover, the broadness and the variety of outcome measures make it difficult to have a clear idea about the state of art. However, given the limited evidence available, it is not possible to draw any firm conclusions about the association between childhood adversity and the functional course of psychosis, also because the effect of adversity on functional outcomes may be independent of its effect on psychosis symptoms. A multi-dimensional definition of outcome is important in the FEP population, where a greater percentage of patients would be expected to respond to antipsychotic medication, despite overall limited social functioning (Sheitman et al., 1997). Often in psychosis the clinical and social/functional aspects do not recover in a parallel way (Ciompi, 1980; Harding et al., 1987;

Liberman et al., 2002a, 2002b; Tohen et al., 2000; Witehorn 2002), and should be assessed separately in reporting outcome (Harrison & Mason, 1993). Defining outcome as multiple, composed of several semi-independent and different areas such as social relations, employment, symptoms and duration of hospitalization might help to clarify this issue and lead us to understand the association between childhood adversity and outcome of psychotic disorder.

Concluding remarks

Although the research literature investigating the link between childhood adversity and development of psychosis has increased in the last few decades, a similar increase in the studies exploring the association between childhood adversity and course of psychosis has not been witnessed. This systematic review suggests that victims of childhood adversity may demonstrate a more persistent symptomatic course of clinical psychosis and worst social outcomes compared to non-victims. However, it should be noted that much of the existing research is methodologically limited and this necessarily urges caution in drawing any firm inferences about the role of adverse childhood events in the course of psychotic disorder. To date, only a few studies have focused on this issue and the broadness and the variety of outcome measures make it difficult to have a clear idea about the state of the art. This review of the literature focusing mainly on clinical and social outcomes demonstrates that there is still a big gap in our understanding of the relationship between adverse childhood experiences and course of psychosis.

Further research is warranted to develop a greater understanding of which individuals with psychosis are likely to have the poorest outcomes and whether this is associated with exposure to different forms of adversity; this would assist clinicians in targeting interventions at those patients with the highest risk of a poor prognosis. Interventions aimed at reducing childhood maltreatment could help prevent the large health and economic burden linked to onset of psychosis and poor illness course. In the same way that childhood

educational interventions represent an investment in human capital formation (Heckman, 2006), early preventive and therapeutic interventions may be more effective in preventing a poor longitudinal course of illness than interventions at later ages.

Utilizing a reasonably-sized catchment-based sample of first-presentation psychosis cases and a representative sample of general population controls from the same geographical locations, I have attempted to address some of these background limitations in this thesis by:

- studying the associations between different types of childhood adversity and onset of psychosis;
- investigating the impact of childhood adversity on the clinical course of psychosis over a one-year period;
- exploring the social functioning of patients that experienced childhood adversity one year after the onset of psychosis.

Specifically, in Chapter 4, I will test the following hypotheses:

- First-episode psychosis patients will be more likely than unaffected controls to report a history of exposure to adverse experiences during their childhood.
- There will be a dose-response effect, such that psychosis cases will report greater exposure to multiple adversities than controls.
- Childhood adversity will be more prevalent in women than in men and in ethnic minority groups.
- Childhood adversity will be more prevalent amongst patients with affective psychosis, and to a lesser extent non-affective psychosis, than controls.
- There will be a certain degree of specificity between childhood adverse events and psychosis symptoms, such that experiences of sexual abuse

will be associated with positive symptoms, experiences of physical abuse will be associated with thought disorder and cognitive disorganization symptoms.

- There will be a higher prevalence of childhood adversities in those controls who report psychotic-like experiences (PLEs) than in those controls who did not report PLEs.
- History of childhood adversity will be associated with a worse clinical and social outcome amongst individuals with psychosis a year after their first contact with mental health services.
- Psychosis cases that reported exposure to multiple types of adversities will have worse clinical and functional one-year outcomes than those who did not report exposure to multiple adversities.

CHAPTER 2 – The interplay between genetic factors and childhood adversity in psychosis

Although the concept that individuals play an active role in selecting, modifying and constructing their environment is widely accepted in evolutionary biology (Dawkins, 1982), traditional models of psychiatric epidemiology often assumed that the relationship between individuals and their environment is unidirectional, from environment to person. However, the causality of this association has been increasingly questioned over the years (Kendler & Baker, 2007). In fact, it is now widely accepted that organisms both impact on and are impacted upon by their environment (Bell, 1968; Wachs & Plomin, 1991).

Many studies have investigated the biological impact of childhood adversity by taking into account genetic differences that trigger the stress response and increase the likelihood of resilience vs. vulnerability following maltreatment (McCrory et al., 2011). Twin and adoption studies have demonstrated that many of the psychiatric disorders that are associated with maltreatment, such as PTSD, depression, and antisocial behaviour, are partly heritable (Koenen et al., 2008; Rhee & Waldman, 2002; Sullivan et al., 2000). Individual differences in susceptibility to these disorders might be explained in terms of genetic variants that act across the lifespan by biasing the functioning of several brain and hormonal circuits, which mediate the body's response to stress (Plomin et al., 1994; Viding et al., 2006).

Therefore, another possible mechanism through which childhood adversity might impact on the development and outcome of psychosis is through interactions with genetic factors. The relative contribution of these factors and the interplay between them has been investigated in terms of gene-environment correlation and gene-environment interaction, using quantitative (e.g., affected relatives) or molecular (e.g., specific polymorphisms) genetic measures.

Gene-environment correlation (rGE)

Gene-environment correlation is when "genotypes are selectively exposed to different environments" (Plomin et al., 1977, p. 309); it refers to genetic mediation of associations between environments and traits (Plomin, 2014). According to this model, individual differences can be explained in terms of variation in the exposure to environmental pathogens which is influenced by genes (Plomin et al., 1977). To refer to GE correlation, Plomin and Bergeman (1991) used the expression "the nature of nurture", as it involves treating environmental measures as dependent measures in quantitative genetic analyses.

There are three types of gene-environment correlation: *passive*, *evocative* and *active*. In the passive form, the genetically related parents provide both a positive or negative rearing environment, e.g. the risk of being abused in childhood is increased by having a biological parent with a psychiatric disorder (e.g., De Bellis et al., 2001; Famularo et al., 1992; Kim-Cohen et al., 2006a; Medley & Sachs-Ericsson, 2009; Mullen et al., 1996; Romero et al., 2009; Walsh et al., 2002; Windham et al., 2004), as well as potentially passing on genetic vulnerability (or resilience) towards development of psychosis in the child. In the *evocative* or *reactive* type, the child elicits responses from others that are influenced by his genotype; e.g., parents may employ harsher methods of physical punishment with children who have a difficult temperament, and in turn the injuries sustained from this may increase the risk for development of psychosis (Lyons et al., 1993). The *active* gene-environment correlation represents the child's selective attention to and learning from aspects of his environment that are influenced by his genotype and indirectly correlated with those of his biological relatives (Scarr & McCartney, 1983). An example of this type of correlation is when individuals with high levels of social anxiety are more likely to choose solitary environments and consequently may be more prone to develop psychosis as they are likely to lack the normalising influence of other people (White et al., 2000). Moreover, it seems that the importance of the three gene-environment correlations changes over the course of development: the

influence of the passive kind declines from infancy to adolescence, with the relevance of the active type increasing over the same period (Scarr & McCartney, 1983).

In the last few decades more than 100 empirical reports that explore the impact of genes on a wide range of environmental measures such as life events, social support, parenting and even children's television viewing have been published. Dozens of twin and adoption studies have shown genetic influence on widely used measures of the environment (Plomin, 1994; Rowe 1981, 1983). A review of 55 genetic studies analysing environmental measures as dependent variables found an average heritability of 27% across 35 different environmental measures (Kendler & Baker 2007), indicating that every aspect of the environment that they examined was significantly influenced by genetic factors. Another recent review of 32 studies on parenting in child-centered designs (i.e., where twins are children) reported an average heritability of 23% (Avinun & Knafo, 2013). Moreover, having one or more biological parents with a history of psychosis has been associated with a greater risk of exposure to stressful life events and adverse experiences during childhood (Alemany et al., 2013; Kramer et al., 2012; Pfeifer et al., 2010) and also with the development of psychotic symptoms and disorders (Schürhoff et al., 2009).

Therefore, GE correlation has important implications for studies assessing environmental effects; this potential confounder is clearly essential to take into account when exploring associations with psychopathology. Its influence also seems to shift from a passive model of the environment imposed on individuals by their parents to an active model in which individuals actively create their own experiences in part on the basis of their genetic propensities (Plomin, 2014).

Gene-environment interaction (GxE)

Another possible mechanism through which childhood adversity might impact on the development and outcome of psychosis is through interactions with genetic factors, which represents the focus of much behavioural genetic research. Risk

factors interact when one factor modifies the effect of another factor on the occurrence of disease (Thompson, 1991). This can happen in two possible ways: when the presence of one risk factor augments the biologic effect of another, the two risk factors are said to have synergistic effects; when the presence of one risk factor reduces, eliminates, or reverses the effect of another, the two risk factors have antagonistic effects (Thompson, 1991).

Specifically, GE interaction indicates the genetic influence on response to environments (Plomin, 2014), a relationship in which the environmental effect on a phenotype depends on genotype (Kendler & Eaves, 1986). It refers to genetic moderation of associations between environments and traits (Plomin, 2014). Differently from active GE correlation model, where individuals select, modify and create experiences that are correlated with their genetic propensities, the GE interaction approach assumes that the influence of an individual's genotype on the disordered outcome depends on environmental exposure and, vice versa, the effect of environmental exposure on risk for a disorder depends on an individual's genotype (European Network of Schizophrenia Networks for the Study of Gene-Environment Interaction, 2008; van Os et al., 2008). Thus the extent to which an individual reacts to the environment is in part based on his/her genetic propensities (Plomin, 2014).

It is important to distinguish between biological interaction and statistical interaction models. Biological synergism refers to the proportion of the population exposed to both genes and environment that developed the illness (e.g., psychosis) because of the combination of these exposures; parallelism refers instead to the proportion of the population exposed to both genes and environment that developed the disease because of either genes or environment (van Winkel, 2008b).

In epidemiology, synergism is measured by multiplicative statistical interaction or by additive statistical interaction (Darroch, 1997). In the case of statistical multiplicative interaction, the effect of genetic predisposition and environment in combination is more than the product of their isolated effects at

the population level (van Winkel, 2008b). Under a multiplicative model, the null hypothesis is that risks for each exposure combine multiplicatively (Risk ratio A and B = Risk ratio A only x Risk ratio B only). If risk when exposed to both A and B is greater, or less than multiplicative, there will be statistical interaction under a multiplicative model (Zammit et al., 2010a; 2010b). Therefore, a multiplicative interaction assumes that individuals who were exposed to both factors cannot have contracted the illness because of the effect of just one of these factors alone.

However, it seems that interactions between putative causal risk factors may be better estimated from the additive statistical interaction model as these more closely approximate biological reality (Darroch, 1997). Under an additive model, the null hypothesis is that risks for each exposure combine additively (Risk A and B = Risk A only + Risk B only – Risk Neither A nor B). If risk when exposed to both A and B is greater, or less than additive, there will be statistical interaction under an additive model (Zammit et al., 2010a; 2010b). Risk factors effects are, in fact, additive on a liability scale.

The liability threshold model (Fig. 2.1) hypothesizes that the members of a population have a normal (Gaussian) distribution of genetic liability for a particular trait; liability for a disease is the sum of many small independent effects (Haegert et al., 2004). Individuals whose genetic liabilities exceed a threshold value are affected by the trait; individuals with liability less than this threshold will never manifest disease. Exposure to environmental factors could shift the disease liability of an individual with genetic vulnerabilities towards or away from the threshold value. An additive approach based on a liability threshold model for psychosis will thus be utilised within this thesis.

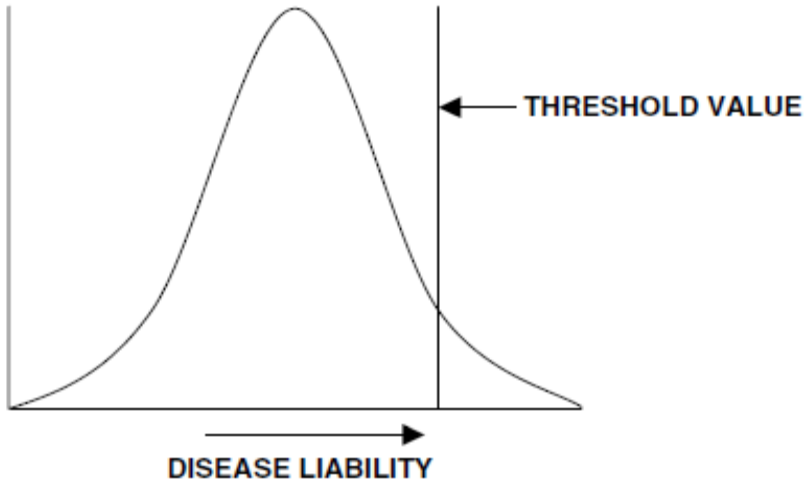

Figure 2.1 The threshold liability model showing the liability distribution for psychosis within a population. According to the model, individuals to the right of the threshold value are affected and those to the left are healthy (Taken from Haegert, 2004).

GxE appears to be particularly relevant for psychotic disorder, given that both environmental and genetic factors have consistently been implicated in its etiology (European Network of Schizophrenia Networks for the Study of Gene-Environment Interaction, 2014). Given that, there is considerable variation in phenotype, as not all individuals exposed to environmental risk or carrying genetic risk variants go on to develop the disorder (European Network of Schizophrenia Networks for the Study of Gene-Environment Interaction, 2014), GxE might account for part of the large discrepancy in heritability estimates from twin and molecular genetic studies (Sullivan et al., 2003; Uher, 2014). However, several challenges still need to be addressed when conducting GxE studies and these include: (a) a validated measure and model of environmental effects; (b) the use of complex GWAS data and genetic variation; and (c) inclusion of different phenotypic levels of psychosis at which GxE may impact (European Network of Schizophrenia Networks for the Study of Gene-Environment Interaction, 2008; 2014).

Probably for these reasons, there is still a limited number of GxE studies on candidate genes in schizophrenia at present (e.g., Caspi et al, 2005; Di Forti et al, 2012; Iyegbe et al., 2014; Modinos et al., 2013; Moffitt et al., 2005), which have attempted to test single-nucleotide polymorphisms (SNPs), with limited evidence on the mechanisms underlying this interaction in psychosis (van Os et al., 2008; 2010).

Childhood adversity, psychosis and familial genetic risk

In the absence of direct genetic data, researchers have used data on various parameters derived from familial aggregation of disorder. These measures of proxy genetic risk range from simple dichotomies, e.g. family history present vs absent, to quantitative metrics, e.g. sibling recurrence risk ratio and heritability estimated from cohorts of twins and families (McGrath et al., 2013). The contribution of genetic factors and/or shared environmental factors within the family to disease risk is suggested by the recurrence of a disorder in different family members.

Attempts can be made to separate contributions of genetic and non-genetic factors by examining the risk of the disorder in certain relatives, such as first-degree vs. second-degree relatives and monozygotic vs. dizygotic twins, and by making assumptions about the degree of shared environment, e.g. twins raised together are more likely to experience similar environments (McGrath et al., 2013). This might help us to better understand the risk architecture of psychotic disorders.

Studies have estimated the heritability of schizophrenia to be at least around 60% (Lichtenstein et al., 2006; 2009), and concordance for schizophrenia in monozygotic twins is around 50% (Cardno et al., 2000). Moreover, having one or more biological parents with a history of psychosis has been associated with a greater risk of exposure to stressful life events and adverse experiences during childhood (Walder et al., 2014; Walsh et al., 2002) and also with the development of psychotic symptoms and disorders (Asarnow et al., 2001;

Polanczyk et al., 2010). This suggests that a 'passive' type of gene-environment correlation (rGE; Plomin et al., 1977) might be operating such that parents provide their children with both an adverse upbringing and a genetic vulnerability to developing psychosis. This implies that parents' genetic make-up may be confounding the childhood adversity-psychosis associations observed in previous studies.

It is also possible that genetic factors moderate the association between childhood adversity and psychosis (a gene-environment interaction [GxE]; Plomin et al., 1977), potentially by influencing how an individual reacts biologically and/or psychologically following exposure to adversity, in such a way as to set them off on the path to psychosis (van Os et al., 2008). Interaction between adversity and genetic liability has been reported (Pfeifer et al., 2010), and early adversity was shown to moderate genetic risk of psychosis outcomes in two adoption studies (Walberg et al., 1997; Wicks et al., 2010). Moreover, Schürhoff et al. (2009) found a significant positive correlation between history of childhood trauma and schizotypal dimensions in unaffected first-degree relatives of schizophrenic subjects. Children considered at high risk (with a schizophrenic parent) seem to be vulnerable to unsatisfactory family relationships.

Tienari et al. (1994, 2004) studied a nationwide Finnish sample of adopted children from mothers with and without schizophrenia. They demonstrated that the risk of developing psychosis in the offspring was higher in the presence of both genetic and environmental risk factors. Other researchers also report increased risk of future psychopathology in high risk children separated from their parents during childhood (Quinton et al., 1984), and, more specifically, increased risk of schizophrenic symptoms. Furthermore, Walker et al. (1989) showed that high-risk children exposed to parental maltreatment reported greater behavioral dysfunction than high-risk children not exposed to parental maltreatment. Finally, evidence suggests that high levels of criticism in the family predict onset of schizophrenia-spectrum disorders in adolescents (Valone et al., 1983).

From another perspective, Burman et al. (1987) supported the idea of a buffering effect of satisfactory family relationships for individuals at genetic risk for schizophrenia, finding a significant association between negative family relationships and risk to develop schizophrenia later in life among the offspring of schizophrenic mothers. Moreover, high risk families tend to perceive and report worse family relationships than low-risk families (Burman et al., 1987; Nettelbladt et al., 1996; Scott et al., 1993; Shiffman et al., 2002). Extending these findings, Schiffman et al. (2002) showed evidence for what they call the "Interactive Hypothesis": genetic liability and poor parent–child relationships together increase risk of offspring schizophrenia. However, they provide a "Genetic Hypothesis" interpretation showing that children with greater genetic liability for schizophrenia have poor relationships with their parents in keeping with the rGE discussed in the previous section. Therefore, high genetic liability seems to lead to both worse family relations and schizophrenic outcome.

However, most of the studies involving familial liability as a measure of proxy genetic risk have been restricted to general population samples and results are still controversial (Alemany et al., 2013; Arseneault et al., 2011; Asarnow et al., 2001; Heins et al., 2011; Pfeifer et al., 2010; Wigman et al., 2012). Arseneault et al. (2011), investigating the risk of developing psychotic symptoms associated with maltreatment in a nationally representative U.K. cohort of twins, reported that children's genetic vulnerability for developing psychotic symptoms, indexed by a maternal history of psychosis or the co-twin's symptoms, was not moderated by the cumulative history of childhood trauma. In their study, maltreatment by an adult and bullying by peers were strongly associated with children's reports of psychotic symptoms independently of the confounding effect of genetic susceptibility to developing psychotic illnesses (Arseneault et al., 2011). The independent effect of childhood adversity on positive and negative psychotic experiences has been demonstrated in a study conducted on monozygotic twins, indicating that this association is not due to genetic confounding (Alemany et al., 2013). Furthermore, in a case-control case-siblings

comparison, Heins et al. (2011) found no evidence of gene-environment interaction, such that an association between trauma and psychosis symptoms was constant regardless of the genetic risk. In line with the previous findings, Wigman et al. (2012) showed that development and persistence of subthreshold psychotic symptoms may be conditional on non-interacting proxy genetic and environmental influences between general parental psychopathology and childhood trauma.

However, only one study has investigated the interplay between childhood adversity and familial risk for mental health problems in a first-episode psychosis sample (Fisher et al., 2014) and found associations between parental history of psychosis and self-reported severe physical abuse from mother before 12 years of age, indicating the potential presence of a passive gene-environment correlation. However, there was no evidence of gene-environment interaction such that individuals who reported exposure to childhood maternal physical abuse were not more likely to have a psychotic disorder if they also had familial liability for psychotic or affective disorders compared with those without this risk factor (Fisher et al., 2014). Nonetheless, this study focused only on one form of childhood adversity and the potential interplay between familial liability and a wider range of childhood adversities still requires investigation.

Illness course in schizophrenia also seems to be influenced by familial factors (Hamshere et al., 2011). Wieselgren and Lindstrom (1996) found a borderline trend for those with a family history of schizophrenia to have worse outcome at one year, but to show greater improvement over years 1 to 5 than those without a family history. Jarbin et al (2003) showed that among patients with schizophrenia-spectrum disorders there was poorer general functioning if there was a family history of non-affective psychosis. However, there are only very few studies of family history and treatment outcome that include first-episode psychosis patients. A positive psychiatric family history has been associated with less reduction in positive and negative symptoms, lower average levels of intellectual functioning and a higher rate of EEG anomalies over time

(Norman et al., 2007) but not with relapse (Caseiro et al., 2012). Moreover, Verdoux et al. (1996) found amongst an admitted sample of recent-onset psychosis patients that greater familial loading for psychotic disorders was associated with more persistent negative symptoms, longer hospital stays and higher levels of social disability. Therefore these findings regarding the significance of family history of schizophrenia spectrum disorders and the genetic impact on the illness course are still inconsistent. Furthermore, no studies to date have explored the moderating role of familial genetic risk in the association between childhood adversity and course of psychosis.

Using family history as a measure of proxy genetic risk

The advantage of using familial liability to psychosis as a proxy for genetic risk is that it may capture a greater proportion of genetic load, including gene-gene interactions, in contrast to studies using direct molecular genetic measures that tend to incorporate only a relatively small contribution to genetic variation in the form of single-nucleotide polymorphisms (SNPs; McGrath et al., 2013). Moreover, despite the advent of polygenic risk scores, which combine multiple SNPs and thus increase the amount of genetic variation accounted for, it is not clear whether these will provide any additional mechanistic clues over and above measures of family psychiatric history because they aggregate information across thousands of SNPs, thus making it difficult to disentangle which combinations of SNPs are driving the interaction (Jaffee & Price, 2012).

It is important to note though that a history of psychosis and other psychiatric disorders in first-degree relatives is only a proxy for genetic risk and may also reflect some aspects of the environment in which individuals are brought up (van Os et al., 2008), though this component is likely to be fairly small (Lichtenstein et al., 2009). Therefore, at present there is no ideal measure of genetic risk to employ in exploring rGE and GxE for psychosis and thus triangulation of evidence obtained from different measures across multiple studies is likely to be the best overall strategy. In summary, family history of

disorder is an important positive predictor and has been informative in schizophrenia research (Agerbo et al., 2012) but the minimal literature on this proxy genetic risk factor in interaction with child adversity has been inconsistent. In light of this, studies investigating the interplay between various forms of childhood adversity and family psychiatric history in the onset and course of psychotic disorders are required. For these reasons, in Chapter 5, I focus on trying to broaden the evidence base in relation to familial liability to psychosis. Specifically, I will test the following hypotheses:

- Family history of psychosis in first-degree relatives will be associated with psychosis in participants.
- Parental genetic risk will partially moderate the association between childhood adversity and psychosis.
- Participants with a family history of mental illness and reported exposure to adverse childhood experiences will be more likely to be psychosis cases than controls.
- The synergistic effect of childhood adversity and familial liability will have an impact on one-year clinical and social outcomes of psychosis.

Childhood adversity by genotype interaction in psychosis

Single SNPs studies

While the genetic contribution to psychosis is well-established, identifying the specific genetic variants involved is still a challenge. A single nucleotide polymorphism (SNP) is a variation which occurs when a single nucleotide exists in different forms, or alleles, at the same locus between individuals. Genetic association studies involve comparing the frequency of alleles between disease and control groups. Putative schizophrenia susceptibility genes include *NRG1* (neuroregulin 1), *DTNBP1* (dysbindin), *DRD1-4* (dopamine receptors D1–D4), *DISC1* (disrupted in schizophrenia 1), *COMT* (catechol-O-methyltransferase), *GRM3* (metabotropic glutamate receptor) (Tandon et al., 2008) and *ERBB4*

(receptor tyrosineprotein kinase) (Stefanis et al., 2013). However, individual genetic variants alone have not been shown to date to account for the development of psychosis or other mental health problems. Therefore, over the past decade, researchers have begun to investigate whether interactions between specific genes and adverse environments may play a role in the aetiology of psychiatric disorders.

The first evidence of a GxE interaction in psychiatric disorders was provided in 2002 by the Dunedin study, which found that maltreated children with a genotype conferring high levels of *MAOA* (monoamine oxidase A) expression were less likely to develop antisocial problems, whereas maltreated children with the genotype conferring low expression were more likely to victimise others (Caspi et al., 2002). This finding has been replicated more recently (Cerdá et al., 2010; Kim-Cohen et al., 2006b; Verhoeven et al., 2012; Wermter et al., 2010).

Several neurobiological pathways have been implicated in psychosis and have provided the candidate genes for association studies. Much focus has been on the serotonergic system. Serotonin (5-hydroxytryptamine, *5-HT*) is a monoamine neurotransmitter that regulates important biological and psychological processes, such as sleep, food intake, pain, vascular tone, platelet function, motor activity, mood and is associated with the development of several psychiatric disorders (Mohammad-Zadeh et al., 2008). The serotonin transporter protein (*5-HTT*), a transporter located on the presynaptic neuron, is responsible for reuptake of the neurotransmitter and represents the primary mechanism for termination of serotonergic neurotransmission.

Genes coding for *5HTT* and polymorphic variants, have become the most investigated in psychiatry and psychology. Previous studies have claimed that the functional polymorphism in the promoter region of the gene (*5-HTTLPR*) is associated with susceptibility to several psychiatric disorders; in particular, the short (s-) allele has been reported to be significantly associated with increased susceptibility to bipolar disorder, anxiety even in neutral situations and post-

traumatic stress disorder, while the long allele has been reported to be associated with completed suicide, alcohol and nicotine dependence and ADHD (Kenna et al., 2012). The serotonin system is also suspected to be possibly involved in the pathophysiology of schizophrenia (Holloway et al., 2013). Recent studies suggested that prefrontal serotonin 2A receptors (*5-HT2ARs*) are linked to the pathogenesis and treatment of schizophrenia and that genotype and changes in nucleotide methylation of the *5-HT2ARs* gene may be contributing to the altered expression of the gene in the Central Nervous System (CNS) of subjects with schizophrenia and bipolar disorder (Abdolmaleky et al., 2011; Santini et al., 2013). It has also been shown that prenatal stress induces schizophrenia-like alterations of *5-HT2ARs* in the adult mice (Holloway et al., 2013).

Moreover, the functional polymorphism in the promoter region of the SLC6A4/5-HTT serotonin transporter gene (*5-HTTLPR*) has also been linked to an altered stress response and increased risk for developing adult psychopathology (Appel et al., 2011; Boscarino et al., 2012; Caspi et al., 2003; Grabe et al., 2010; Roy et al., 2012; White et al., 2012; Xie et al., 2010). Carriers of the short (s-) allele were reported to have increased negative psychological reactions to severe life events including childhood trauma, such as more depressive symptoms, diagnosable depression and suicidality, compared with carriers of the long (l-) allele (Caspi et al., 2003). However, meta-analytic studies have reported contradictory results (Karg et al., 2011; Risch et al., 2009).

Specifically, it appears that childhood maltreatment may lead to atypical responsiveness of the HPA axis to stress, which in turn predisposes to psychiatric vulnerability in later life (McCrory et al. 2011; van Goozen & Fairchild, 2008). Indeed, previous research reported that stress sensitivity and activity of the HPA axis secretion may be relevant to the development of psychiatric vulnerability in adulthood and the expression of psychotic disorders such as schizophrenia (Rosenthal, 1970; Walker & Diforio, 1997). The *FKBP5* gene, in particular, has

been reported to moderate sensitivity to childhood adversity and it has also been linked with HPA axis.

Several single nucleotide polymorphisms (SNPs) in *FKBP5* have been found to increase *FKBP5* protein expression and have been related to treatment response in patients with mood disorders (Cheng et al., 2006; Binder, 2009; Horstmann et al. 2010; Koenen et al., 2005; Shibuya et al. 2010; Tatro et al. 2009). It has been shown that *FKBP5* polymorphisms are associated not only with differential HPA axis function but also with psychopathology in the context of stress (Table 2.1; taken from White et al., 2012).

Moreover, the *FKBP5* gene has been shown to interact with childhood abuse and trauma to predict risk for developing adult psychopathology like suicidal behaviour (Roy et al., 2012), PTSD (Binder et al., 2008; Boscarino et al., 2012, Xie et al., 2010) and adult depression (Appel et al., 2011; Grabe et al., 2010; White et al., 2012). Recent research also showed that *FKBP5* interacted with childhood emotional neglect to predict heightened threat-related dorsal amygdala reactivity (White et al., 2012). While *FKBP5* genotype alone may have a modest effect on amygdala reactivity, it will be interesting to investigate the role of environmental stressors that lead to significant bias in reactivity. This reactivity bias in the context of emotional neglect may represent a mechanism through which individuals carrying these *FKBP5* alleles show an increased risk for stress-related psychopathology (White et al., 2012).

Table 2.1 Associations between *FKBP5* Polymorphisms, stress responsiveness and psychopathology (Taken from White et al., 2012).

SNP (Location)	Association
rs1360780 (Intron)	T allele: Increased *FKBP5* protein levels; reduced basal levels of cortisol; impaired HPA negative feedback following dexamethasone (DEX) and psychosocial stress; PTSD symptoms, incidence of depression, depressive symptoms and suicide in the context of childhood maltreatment; increased depression recurrence and more rapid response to antidepressant treatment; increased harm avoidance and reduced cooperativeness (Binder et al., 2004, Binder et al., 2008, Ising et al., 2008, Shibuya et al., 2010, Xie et al., 2010, Brent et al., 2010, Velders et al., 2011, Appel et al., 2011, Zimmermann et al., 2011)
rs9296158 (Intron)	A allele: Impaired HPA negative feedback of following DEX; reduced *FKBP5* downregulation with increasing PTSD severity; PTSD symptoms and incidence of depression in the context of childhood maltreatment (Binder et al., 2008, Xie et al., 2010, Mehta et al., 2011, Zimmermann et al., 2011)
rs9470080 (Intron)	T allele: Depressive symptoms; reduced basal cortisol levels; PTSD in the context of adverse environmental exposure; incidence of depression in the context of childhood maltreatment (Boscarino et al., 2011, Velders et al., 2011, Xie et al., 2010, Zimmermann et al., 2011)
rs3800373 (3' UTR)	G allele: Increased rate of suicide among depressed individuals; more rapid antidepressant response; increased peri-traumatic dissociation following trauma; increased PTSD and incidence of depression in the context of childhood maltreatment; impaired negative feedback of cortisol following psychosocial stress (Binder et al., 2004, Brent et al., 2010, Koenen et al., 2005, Ising et al., 2008, Zimmermann et al., 2011)
rs7748266 (Intron)	T allele: Reduced basal cortisol levels (Velders et al., 2011)
rs9394309 (Intron)	G allele: Reduced basal cortisol levels (Velders et al., 2011)

Other genes have also been investigated in psychosis. Particularly, childhood adversity has been associated with reduction of brain-derived neurotrophic factor (*BDNF*) levels, both in schizophrenia and bipolar disorders (Kauer-Sant'Anna et al., 2007; Mondelli et al., 2011). *BDNF* is a protein encoded by the *BDNF* gene and supports survival and growth of neurons. *BDNF Val66Met* is a common variation in the *BDNF* gene and *Met*-carriers of this polymorphism have decreased secretion of *BDNF*. Studies conducted on a large group of patients with schizophrenia, bipolar disorder and major depressive disorder (Aas et al., 2013; 2014) showed that *Met* carriers are more vulnerable to the negative effect of childhood trauma and reported stronger negative affective responses to social stress compared to the *Val/Val* carriers (van Winkel et al., 2014).

A dopamine system related gene for psychosis is the *COMT* (catechol-O-methyltransferase) gene, which has been recently associated with the stress response. Three studies of the interaction of the *COMT Val158Met* genotype and stress reactivity have shown increased symptoms in response to stress in psychotic individuals homozygous for the *Met* allele (Collip et al., 2011; Peerbooms et al., 2012; van Winkel et al., 2008a). Another study found more severe positive symptoms in *Met* carriers who had experienced physical abuse, and greater severity of negative symptoms in *Met* carriers in the presence of emotional neglect (Green et al., 2014).

A gene involved in dopamine signalling transmission, which has also been reported to be associated with schizophrenia is the *AKT1* gene, located on chromosome 14q32 (Freyberg et al., 2010; Mathur et al., 2010). A GxE interaction has been reported between an *AKT1* gene polymorphism, rs2494732, and an environmental risk factor, such as cannabis use, in the pathogenesis of psychosis: carriers of the *C/C* genotype were most likely to develop psychotic illness after smoking cannabis (Di Forti et al., 2012; van Winkel et al., 2011a, 2011b). To date, no studies investigated the effect of *AKT1* gene x childhood adversity interaction in psychosis onset and its clinical and functional outcomes. A pilot study focusing on the potential relationship of stress and psychosis showed that higher subclinical psychotic experiences were associated with chronic and severe stress and *AKT1* SNP rs2494732 in a sample of students (Bruenig et al., 2014). Therefore, it would be interesting to investigate the possible interaction between these two dopamine genes, *AKT1* and *COMT*, and childhood adversity in psychosis.

Furthermore, genotypes represent predictors of both risk and resilience for adult psychiatric disorders for people with a history of childhood adversity. A recent line of research also emphasizes the protective role of positive environmental influences, i.e. social support, for the risk to develop psychopathology and the promotion of resiliency (McCrory et al., 2011). Kaufman et al. (2006) showed that maltreated children with the *Met* allele of the

BDNF gene and two short alleles of *5-HTTLPR* had the highest depression scores, but they were less likely to develop depression if they had social support. These findings highlight the importance of positive early environmental influences, such as the presence of a supportive attachment figure, and their protective role even in the context of genetic vulnerability. Therefore, despite at present several main genes showed an association with schizophrenia, the G-E interaction with specific childhood adversity need to be further explored.

Rationale for the selected genetic predictors

A difficult challenge is to identify plausible susceptibility genes to investigate how, and if, they moderate the effect of childhood adversity on the risk of psychosis. Genes involved in regulation of dopamine levels in the brain (e.g., catechol-O-methyltransferase [*COMT*]: Garris et al., 1993; serine/threonine-protein kinase [*AKT1*]: Freyberg et al., 2010) and of the hypothalamic-pituitary-adrenal (HPA) axis (e.g., glucocorticoid receptor co-chaperone [*FKBP5*]: Collip et al., 2013) would be plausible biological candidates for interaction with childhood adversity due to their link with psychosis (Bolog et al., 2012; Cheng et al., 2006; Egan et al. 2001; Karege et al., 2012; Li et al., 1996; Norton et al., 2007; Thiselton et al., 2008). Therefore, in this study, I selected known genotype variants of *COMT*, *AKT1* and *FKBP5* genes, which have been shown to impact on the dopamine and HPA axis systems, to investigate if they interact with childhood adversity to increase the risk of psychosis disorder. The novelty of my study is also evident by the focus on whether such GxE interactions have an impact on the clinical course and social outcomes of psychosis over the first year of illness.

COMT Val158Met

COMT plays an important role in the metabolism of catecholamines, such as dopamine and norepinephrine, in the central nervous system. A single nucleotide polymorphism (472G/A) in the *COMT* gene, located on chromosome 22q11.2 (Winqvist et al., 1991), causes an amino acid change from valine to

methionine at position 158 (*Val158Met*), with a 3- to 4-fold variation in enzymatic activity (Chen et al., 2004a; Weinshillboum et al., 1999) between *Val/Val* (or equivalent *G/G*) genotype and *Met/Met* (or equivalent *A/A*) genotype. Specifically, *Met/Met* genotype carriers have the lowest COMT activity, *Val/Met* hetheterozygotes have an intermediate activity whereas the *Val/Val* carriers are those with the most enzyme activity (Mannisto & Kaakkola, 1999).

Diverse gene-environment interactions have been reported for *COMT Val158Met* in moderating risk for psychotic disorder (Bilder et al., 2004; Tunbridge et al. 2006), for example, in the case of cannabis use in adolescence (Caspi et al., 2005; Henquet et al., 2009) and daily life stress (Peerbooms et al., 2012). Specifically, the *Val* allele has been associated with self-reported psychotic experiences in the context of stress and cannabis use in a Dutch adult population sample (Vinkers et al., 2013) and with the stress of army induction in a Greek male conscript sample (Stefanis et al., 2007). *COMT Val158Met* has also been associated with increased schizotypal personality trait scores in *Val/Val* individuals exposed to higher levels of self-reported childhood trauma (Savitz et al., 2010). Additionally, chronic low-level stressors appear to interact with the *COMT Val158Met* polymorphism to increase the intensity of psychotic experiences in those already diagnosed with the disorder (Myin-Germeys et al., 2006). However, in this latter study it was the *Met/Met* genotype that conferred risk whereas in previous studies the *Val/Val* genotype has been implicated (e.g., Caspi et al., 2005).

In terms of effect on illness course, *Met/Met* homozygous patients had higher aggressive behaviour compared to *Val/Val* homozygous subjects in a 6 year follow-up cohort of patients with schizophrenia (Tosato et al., 2011). Nevertheless, *COMT Val158Met* polymorphism did not show any significant effect in early therapeutic response to antipsychotic medications in paranoid schizophrenia patients (Tybura et al., 2012). Furthermore, no association between this *COMT* polymorphism and levels of clinical symptoms of patients

with chronic schizophrenia was found (Herken et al., 2003; Numata et al., 2007; Strous et al., 2006). Conversely, having the *Met* alleles of the *COMT Val158Met* polymorphism has been found to be associated with remission in patients with depression (Gudayol-Ferré et al., 2013) and reduced risk of experiencing psychotic features during one year course of bipolar disorder (Benedetti et al., 2010). In contrast, the *Met* (low activity) *COMT* allele was associated with rapid-cycling in a sample of patients with bipolar disorders (Kirov et al., 1998). Another study did not found any effect of *COMT Val158Met* genotype on the clinical course of recurrent mood disorders (Cusin et al., 2002).

Therefore, given some evidence of interplay between this candidate polymorphism with environmental risk factors, I decided to investigate the synergistic effect of *COMT Val158Met* polymorphism and childhood adversity on risk of psychotic disorders and its impacts on one-year outcomes.

AKT1 rs2494732

Another candidate to test for a gene x childhood adversity interaction is the *AKT1* gene, located on chromosome 14q32, which has been reported to be associated with bipolar disorder (Toyota et al., 2003) and, more recently, with schizophrenia (Freyberg et al., 2010; Mathur et al., 2010). The *AKT1* codes for a protein kinase (Protein kinase B, PKB), that forms an integral part of a signaling cascade mediating dopamine signaling. Furthermore, *AKT1* appears not only to be involved in psychosis but also to impact risk for a class of a broader clinical phenotypes that include mood dysregulation (Thiselton et al., 2009). One study also evidenced the influence of this gene on prefrontal brain networks during active cognitive processing in patients with schizophrenia (Tan et al., 2009).

An investigation of 152 genetic variants in 42 selected candidate genes (van Winkel et al., 2011a) identified a polymorphism (rs2494732) in the *AKT1* gene that interacted with an environmental factor, namely cannabis use, in the pathogenesis of psychosis with carriers of the *C/C* genotype on rs2494732 most likely to develop psychotic illness after smoking cannabis. This interaction was

been replicated across three analyses in the primary report (van Winkel et al., 2011b) as well as subsequently in the GAP study (Di Forti et al., 2012). In light of these findings, I followed a hypothesis driven approach conducting the GxE analyses for the rs2494732 polymorphism of the *AKT1* gene in interaction with childhood adversity.

FKPB5 rs1360780

The *FKBP5* gene has been reported to moderate sensitivity to childhood adversity and it has also been linked with the HPA axis. It is located on chromosome 6p21, a chromosomal region associated with bipolar disorder and psychosis (Simons & van Winkel, 2013), and consists of 10 exons. It codes for FK506-binding protein 51 (*FKBP5*), a member of the immunophilin protein family, which play a role in immunoregulation and basic cellular processes involving protein folding and trafficking. *FKBP5* also regulates the glucocorticoid-receptor (GR) sensitivity (Binder, 2009). Specifically, cortisol induces the *FKBP5* expression by activation of glucocorticoid-response elements (Vermeer et al, 2003). In turn, *FKBP5* binding to the GR reduces the GR affinity for cortisol and diminishes the amount of activated GR translocation to the cell nucleus (Wochnik et al., 2005). Binder's pioneering study (Binder et al., 2004) reported a C/T single nucleotide polymorphism in the intron 2 of the *FKBP5* gene (rs1360780). The T allele of this polymorphism is associated with higher levels of *FKBP51* protein and with less suppression of cortisol to the dexamethasone test, as well as to slower recovery of cortisol response to a psychological stress test in healthy subjects (Ising et al., 2008).

Although the exact mechanism still remains unclear, it is accepted that this polymorphism influences *FKBP51* protein levels through translation or protein stability. These studies suggest that the T allele is associated with higher levels of the immunophilins leading to impaired negative feedback of the HPA axis (Galigniana et al., 2012). In line with the pathophysiological model, further studies confirmed that the high-induction alleles of the *FKBP5* gene are

associated with a relative GR resistance (Appel et al., 2011; Binder et al., 2008). In synthesis, elevated *FKBP51* levels, leading to reduced GR sensitivity to circulating cortisol, result in a decreased negative feedback regulation of the HPA axis and a slower resolution of the stress response (Binder, 2009).

The *FKBP5* rs1360780 SNP has been reported to sensitise individuals to developing post-traumatic stress disorder after being exposed to childhood maltreatment (Binder et al., 2008; Ising et al., 2008; Uher et al., 2014). There are currently only a few published studies that investigated the role of FKBP5 x childhood adversity interaction in psychosis. Gawlik et al. (2006) tested for an association of rs1360780 with affective psychosis, in a study that controlled for group differences in gender, but did not model environmental co-factors. Collip and colleagues (2013) found a gene–environment interaction between rs9296158 and rs4713916 *FKBP5* SNPs and childhood maltreatment in increasing the risk of experiencing psychotic symptoms in young adults. Ajnakina et al. (2014) reported a significant association at rs1360780 with first-episode psychosis only after adjusting for two environmental factors, cannabis use and parental separation, in the model (OR=2.81, p=0.02). A statistical interaction between rs1360780 and parental separation was confirmed by stratified tests (OR=2.8, p=0.02 vs. OR=0.89, p=0.80). Interestingly, a 10-year prospective community study found an interaction between *FKBP5* rs1360780 SNP and early adverse events but not for separation in predicting the onset of depression (Zimmerman et al., 2011).

The literature investigating the effect of *FKBP5* on illness course has mainly focused on mood disorders and Posttraumatic Stress Disorder (PTSD). Lekman et al. (2008) found an association between rs1360780 SNP with depression in a White non-Hispanic sample but no association with the number of illness episodes or treatment response at 14 weeks. Furthermore, the same SNP has shown to be involved in the course of bipolar disorder with psychotic features in terms of increase of suicidal attempts in carriers of the risk allele (Leszczyńska-Rodziewicz et al., 2014). In a sample of patients with PTSD, carriers

of the rs1360780 risk (*T*) allele were at increased risk of symptom relapse, whereas non-carriers showed continuous symptom reduction at 10 month follow-up (Wilker et al., 2014). Therefore, I sought to replicate the findings on the association between *FKBP5* rs1360780 SNP and childhood adversity in increasing the risk of psychosis onset and to further investigate their synergistic effect on one-year outcomes.

Potential pathways from genetic vulnerability to psychosis

Dysregulation of both the HPA axis and the dopamine system have been postulated to be important in the pathogenesis of psychosis (Howes et al., 2009; Kapur, 2003; Moore et al., 1999; Spitzer, 1995; Walker & Diforio, 1997; Walker et al., 2008) and, as I have illustrated in Chapter 1, have also been independently associated with childhood abuse (De Bellis et al., 1994, 1999; Gerra et al., 2007, 2009; Heim et al., 2000; King et al., 2001; Pruessner et al., 2004; Putnam et al., 1991; Steiger et al., 2001). The fact that exposure to childhood adversity has shown to be associated with psychotic disorder in *COMT Val* carriers could in theory be explained by sensitization involving dopaminergic signalling (Alemany et al., 2013; Collip et al., 2008). Disruptions in postnatal rearing conditions can lead to profound and lasting changes in the responsiveness of mesocorticolimbic dopamine neurons to stress and in animals (Brake et al, 2004; Hall et al., 1999; Pani et al., 2000) as well as in humans (Pruessner et al, 2004). According to the social defeat hypothesis, long-term exposure to the experience of social defeat or social exclusion may lead to sensitization of the mesolimbic dopamine system (and/or increased baseline activity of this system) and thereby increase the risk for schizophrenia (Cao et al., 2010; Selten et al., 2013, van Nierop et al., 2014b). Therefore, exposure to childhood adversity might "sensitize" a person with genetic vulnerabilities to psychosis towards other stressors which, in turn, correspond to exaggerated emotional response at a behavioral level (Myin-Germeys et al., 2001) and to an imbalance of the dopamine neurotransmission between prefrontal cortex (PFC) and mesolimbic circuits (Deutch et al., 1990),

facilitating the onset of psychotic symptoms (Goto et al., 2007; Kapur, 2003; Kapur et al., 2005).

The *AKT1* gene influences the post-receptor dopamine system and is important for emotion regulation (Salgado-Pineda et al., 2005). It has been extensively studied for its role in psychotic disorders (Egan et al., 2001; Karege et al., 2012). The effect of *AKT1* genotype on dopamine regulation might consequently impacts on emotional expression; characteristics of both psychosis patients and victims of childhood adversities (Mandal et al., 1998; Morrison et al., 1988; Powers et al., 2015).

Adverse childhood experiences may also affect dopamine systems indirectly via interactions with dysregulated HPA function that leads to hypercortisolaemia (Buchmann et al., 2014; Charmandari et al., 2003; Corcoran et al., 2003; Green et al. 2014). Glucocorticoids are known to augment the action of dopamine in brain regions such as the mesolimbic system and the striatum (Czyrak et al., 2003; Dallman et al., 2004; Marinelli et al., 2006). *FKBP5* polymorphisms are known to regulate the cortisol binding affinity and nuclear translocation of the glucocorticoid receptor and polymorphisms at the *FKBP5* locus have been reported to interact with exposure to child adversity in predicting PTSD (Boscarino et al., 2012).

In relation to this theoretical framework, in Chapter 6 I will test the following hypothesis:

- Participants with at least one copy of the risk allele of the *COMT*, *AKT1* and *FKBP5* polymorphisms and reported exposure to childhood adversity will be more likely to have psychosis than participants exposed to adversity who carry the non-risk allele.

- A gene by childhood adversity interaction model will provide a better prediction of one-year clinical and social outcomes amongst psychosis patients than either risk factor alone.

Polygenic risk score studies

In psychiatry, gene-environment interactions have been investigated usually selecting single candidate genes based on their hypothesised involvement in the disorder or response to the exposure of interest. However, it seems very difficult to select the correct gene (Collins et al., 2012). Furthermore, GxEs may involve multiple genetic variants rather than one specific locus, particularly for a highly polygenic disorder such as psychosis. Considerable progress in molecular genetic research in psychosis has been made in recent years through large-scale collaboration in genome-wide association studies (GWAS), which have generated replicated findings on a number of common risk alleles (Corvin et al., 2013; O'Donovan et al., 2008; Owen et al., 2010; Purcell et al., 2009; Ripke et al., 2013). GWAS identify differences in allele frequencies between disease and control groups, at hundreds of thousands or millions of SNPs across the entire genome.

Recent advances have further produced consistent findings that rare copy number variants (CNVs) increase schizophrenia risk more than individual common risk alleles identified by GWAS (Grozeva et al., 2010; Guha et al., 2013; Lee et al., 2012; Malhotra & Sebat, 2012). However, the common variants identified to date explain only a small proportion of the genetic risk of schizophrenia and a large number of common risk alleles, with small effects, remain to be identified (Lee et al., 2012; Owen et al., 2012; Purcell et al., 2009).

Therefore, the examination of single SNPs and environmental factors one at a time has been overshadowed by the highly polygenic nature of schizophrenia (Lee et al., 2012; Wray et al., 2010). The international Psychiatric Genomics Consortium (http://pgc.unc.edu/) brought together large sample sizes for schizophrenia, leading to important results (Sullivan et al., 2012a; 2012b). Specifically, polygenic risk scores are obtained after carrying out a Genome Wide

Association Study (GWAS) in a discovery sample. Then a polygenic risk score for each individual in an independent target sample is derived by counting the number of risk alleles for each SNP weighted by the effect size drawn from the discovery sample. SNPs up to a certain threshold of significance, usually ranging from P<0.01 to P<0.5, are taken to predict psychosis in the target sample (Iyegbe et al., 2014; Purcell al., 2009).

However, despite the statistical tools being in place to study G × E in large data sets, the progress is limited by the availability of environmental risk factors recorded in a uniform manner across large and disparately collected cohorts (McGrath et al., 2013).

Recently, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) has published the results of the analysis of all available schizophrenia samples with GWAS data. They identified 108 schizophrenia-associated genetic loci, 83 of which have not been previously implicated in schizophrenia, highlighting potential new biological pathways into disease aetiology. Moreover, the Molecular Genetics of Schizophrenia Study published recently its results that 42 SNP sets were associated with a 70% increased risk of schizophrenia, and confirmed 34 (81%) or more with similar high risk of schizophrenia in two independent samples (Arnedo et al., 2015).

However, very few studies have so far investigated the effect of the association between polygenic score and childhood adversity in psychiatric illness. Peyrot et al. (2014), in a longitudinal cohort study of depressive and anxiety disorders, found that that the polygenic risk scores have limited impact in predicting major depressive disorder risk in individuals with no/low exposure to childhood trauma, but a significant impact in individuals with high exposure to childhood trauma with an OR of 1.16 (p=0.005). Another study drawn from a representative sample of adolescents participating in the National Longitudinal Study of Adolescent Health (Wickrama et al., 2014), showed that individuals with more risk alleles interacted with parental rejection to influence the occurrence of

precocious life transition events (such as completing one's education, beginning a career, and entry into family responsibilities).

Using polygenic scores has several distinct advantages: they can be applied to the whole population of cases and controls; they provide a valid continuous measure of genetic liability on an individual level rather than the dichotomous or categorical measure of family history; and they make it possible to have greatly enhanced power to study the confounding, mediation as well as interaction impact of G with E (McGrath, 2013). Increasing understanding of the polygenic architecture of psychosis liability will enhance studies exploring the environmental causes of this disorder. However, using a polygenic risk score measure may limit the understanding of the mechanisms underlying gene-environment interplay because polygenic risk scores aggregate information across thousands of SNPs. Therefore, this thesis will incorporate both the traditional single gene approach as well as a pilot investigation of polygenic risk score by childhood adversity interactions.

To the best of my knowledge, no research on GxE interaction has focused on polygenic risk score by childhood adversity in psychosis thus far. Therefore, in Chapter 7, I will test the following hypothesis:

- Higher polygenic risk for schizophrenia will be associated with psychosis case status in this GAP subsample.

- The "polygenic risk score" x "childhood adversity" interaction model will better predict an individual's odds of psychotic disorder than the single candidate gene x childhood adversity interaction model.

CHAPTER 3 - Methodology

Introduction

The data presented within this thesis is drawn from the baseline National Institute of Health Research (NIHR) Biomedical Research Centre (BRC) Genetics and Psychosis (GAP) study. Therefore, in this chapter I will outline the study design and the participants' recruitment strategy. This is followed by an outline of the main assessment measures employed in this study and a detailed account of the assessment tools relevant to the analyses undertaken in this thesis. The specific aims are to:

1. Provide an overview of the GAP study and the procedures used to recruit psychosis patients and community controls and main baseline assessment tools.

2. Describe the development, components and scoring procedures for the Childhood Experience of Care and Abuse Questionnaire (CECA.Q) (section 3.2) and one-year follow-up assessment measures.

3. Summarize the statistical analyses applied to test the project hypotheses.

Methodology of the GAP Study

The GAP study was initially a cross-sectional study investigating the role of a number of social and biological factors in the development of psychosis, using a case-control design. In this type of study design participants are selected on the basis of whether they have or do not have the outcome of interest (in this case, first-presentation to mental health services for psychosis), which allows

hypotheses concerning potential risk factors for a disorder to be investigated by comparing the prevalence of "exposures" in those with and those without the "outcome" of interest. The initial baseline study began recruitment of patients and unaffected matched controls in 2005. A one year electronic records-based follow-up of the original psychosis cases and controls was started in 2011. The data utilised in this thesis is drawn from the original baseline study and thus recruitment and assessment procedures for this aspect of the study are described below along with details of the follow-up conducted. Ethical approval was obtained from the NRES Committee London – Camberwell St Giles (Protocol: 05/Q0706/158).

Recruitment of psychosis cases

All patients who presented for the first time to mental health services for psychosis in tightly defined catchment areas in South-east London (Lambeth, Southwark, Lewisham and Croydon), including adult community mental health teams, inpatient units, forensic services, learning disability services and drug and alcohol units of the South London and Maudsley Mental Health NHS Foundation Trust (SLAM), between December 2005 and October 2010, were identified.

Inclusion criteria for the study were applied as follows:

(i) aged between 18 to 65 years old;
(ii) first ever contact (within six months) with mental health services for psychosis;
(iii) presence of psychotic symptomatology for at least a week that was not due to organic psychosis or to acute intoxication, as defined by ICD-10 (World Health Organization, 1992a).

Patients were excluded from the study if they met any of the following criteria:

(i) moderate or severe learning disabilities defined as an IQ less than 70;
(ii) diagnosis of organic psychosis;

(iii) inability to give an informed consent because of insufficient proficiency in English or any other reason;

(iv) previous contact with mental health services for psychosis; or

(v) transient psychotic symptoms resulting from acute intoxication following the administration of alcohol or other psychoactive substance as defined by ICD-10 (World Health Organization, 1992a).

A team of trained researchers weekly screened all in-patient and out-patient mental health services in the catchment areas to identify eligible cases; this was done either by visiting the wards or using an electronic patient record system, called the electronic Patient Journey System (ePJS), provided by the SLAM. PJS is a comprehensive record of all clinical information recorded throughout patients' journeys through Trust services, including demographic and contact information, dates and other details of referrals and transfers, detailed clinical assessments, care plans and medication, clinical activity and reviews. All admissions are also logged on this system. The record is used and maintained by multi-disciplinary professionals and consists of both structured data (such as dates, integers and pick-lists) and unstructured free text (including written assessments, progress notes and correspondence). The electronic patient record was introduced with the goal to share detailed care record of each patient in order to provide better patient information and to improve cost efficiency and reliability of information for quality control and health services planning. When information was either not sufficient or unclear, presence of psychotic symptoms was ascertained by consulting clinical staff.

Eligible patients were screened by administering the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; World Health Organization 1992a). The SCAN interview was used to cover symptoms present for the month before assessment (present state). All patients who met ICD-10 criteria for a diagnosis of non-organic psychosis (F20-F29 and F30-F33) validated by the SCAN were invited to participate: first a complete description of the study was given

(see information sheet in Appendix VI) and only after signing the consent form (see Appendix VII) the assessment started. If potential cases were too unwell to cooperate, they were re-contacted once following initiation of treatment. Potential cases were approached as soon as possible after first contact was made with psychiatric services for psychosis. The mean length of time between first contact with psychiatric services and assessment was 40 days (SD=53), with a median length of 20 days.

Fig. 3.1 illustrates the GAP attrition rate of patients and those included in this thesis.

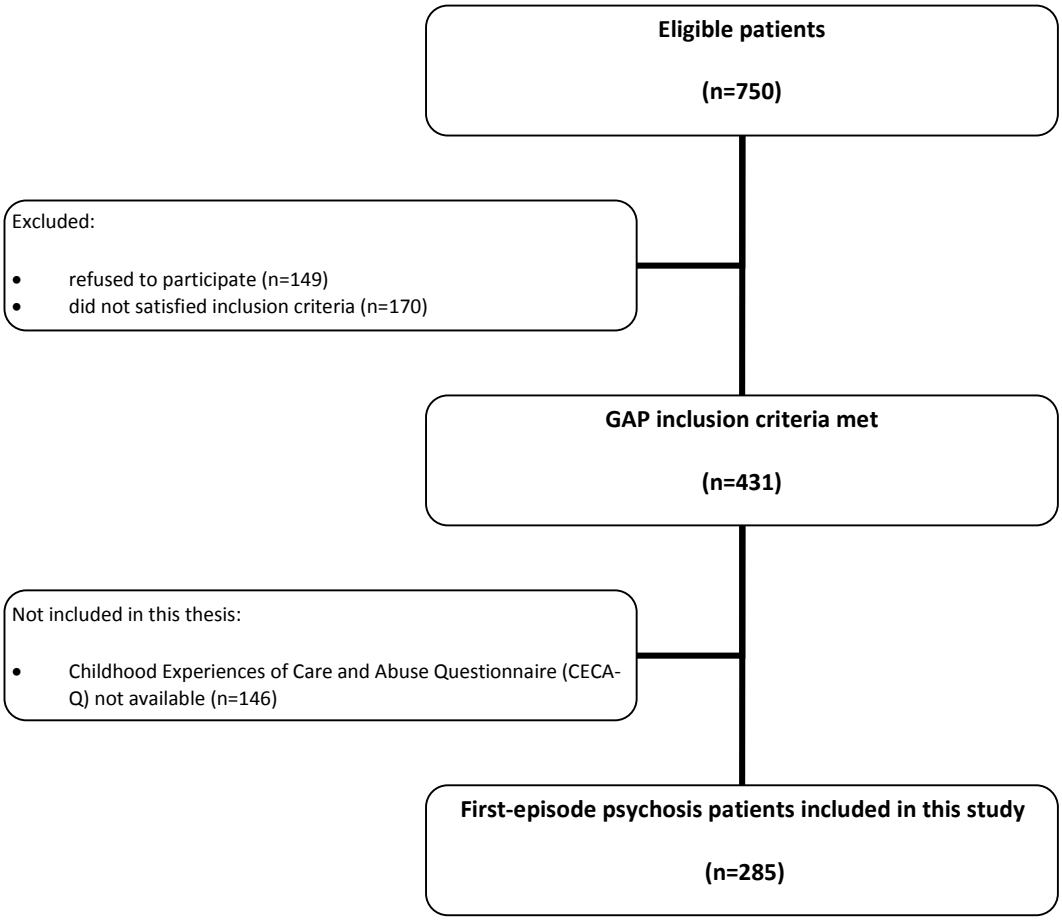

Figure 3.1 Flow chart documenting cases recruitment for the GAP study

Of a total of 750 cases that were approached, 20% (149) refused to participate. As part of a small project nested in the overall study, twelve refusers were interviewed and asked why they were not interested in taking part in the study (Table 3.1).

Table 3.1 Findings of the qualitative study nested into the GAP project, which aimed to identify barriers to participation to the study.

	Consenters M (9) F (8)	**Refusers** M (4) F (5)
Average Age	26.3 (Range 20-33, SD 3.55)	30.2 (Range 20-53, SD 7.8)
Ethnicity		
White British	4	1
Black British	4	2
Black Caribbean	3	1
Black African	2	4
White Irish	1	1
Chinese	1	
Indian	1	
Brazilian	1	

- Semi-structured interviews conducted with patients who had either consented or refused to participate in the GAP study.
- All consenters approached for this study agreed to be interviewed.
- Twelve refusers were approached and three declined participation.
- Of the nine refusers who were interviewed, two initially consented but then refused to participate in any research activities and one consented and completed some assessments but then refused further involvement.

The two most common reasons for refusal were lack of interest in the research and the length of our study assessment. Moreover, refusers were more likely to be of Black Caribbean and Black African origin and of male gender compared to those who consented. Both ethnicity and gender are controlled for as covariates in all the analyses in this thesis. A total of 431 first-episode psychosis patients (57%) met the inclusion criteria of the GAP study. A total of 285 patients (66%)

completed the Childhood Experiences of Care and Abuse Questionnaire (CECA-Q) and thus were included in this thesis.

Recruitment of community controls

Over the same time frame, from the area served by the same mental health units, a control sample which was broadly similar to the local population for age, gender, ethnic distribution, educational attainment and employment status (www.statistics.gov.uk/census2001) was obtained, in the assumption that if they developed a psychotic episode they would have been eligible as cases. Recruitment of controls was done through different ways: internet and newspaper adverts and distribution of leaflets in the area of interest. Control exclusion criteria were: (i) IQ<70; (ii) previous diagnosis or treatment of psychotic illness; (iii) resided outside of the catchment area; (iv) inability to give informed consent because of insufficient proficiency in English or any other reason.

Potential controls that were willing to take part in the study were asked to read a detailed information sheet (see Appendix VIII) and sign a consent form (see Appendix IX). Control participants were first administered the Psychosis Screening Questionnaire (PSQ) (Bebbington & Nayani, 1995) to assess psychotic symptoms in the past year and check for a history of psychosis. Controls who reported one or more psychotic experience within the past year were considered to form a subclinical psychosis group. Subjects who reported a history of psychotic symptoms were still included in the study unless they reported having received a diagnosis of a psychotic disorder and received treatment for it.

Figure 3.2 illustrates controls recruitment for the GAP study.

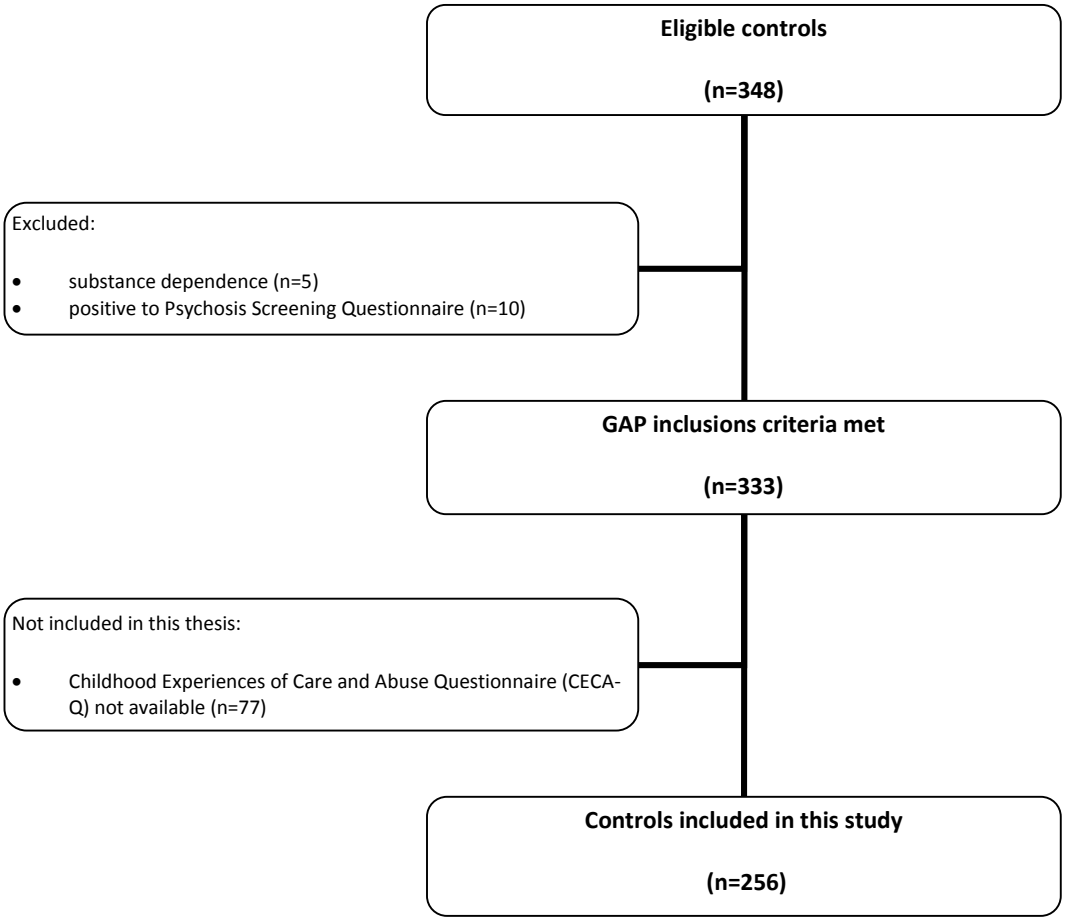

Figure 3.2 Flow chart documenting controls recruitment for the GAP study.

A total of 348 controls were contacted to participate (because of the mode of recruitment none refused to participate). A total of 10 controls willing to take part in the study were excluded because they screened positive on the Psychosis Screening Questionnaire. A total of 5 controls were excluded for substance dependence (heroine and alcohol), which posed a safety issue to the interviewers, as they appeared intoxicated.

Thus, 333 controls were successfully recruited. A total of 256 (77%) completed the Childhood Experiences of Care and Abuse Questionnaire (CECA-Q) and were included in this thesis.

Representativeness of the sample

Missing data are unavoidable in epidemiological and clinical research. Many, epidemiologic studies suffer from missing values on some variables and subjects (Greenland & Finkle, 1995). The risk of bias due to missing data depends on the reasons why data are missing and are commonly classified as: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR) (Sterne et al., 2009).

A common concern when faced with multivariate data with missing values is whether the missing data are missing completely at random (MCAR); in the sense that missingness does not depend on the variables in the data set subject to analysis. However, Wacholder (1995) suggested that a case-control study can be seen as a study in a cohort with some missing exposure data. The epidemiologist's assumption of appropriate selection of cases and controls from the cohort or base is equivalent to an assumption of missing at random: values of covariates for those who develop the disease under investigation do not depend on whether the person is included as a case in the study, and the values of those who do not develop the relevant disease are assumed to be independent of whether or not the person is included as a control (Wacholder, 1995).

An advanced method to test for the missing at random assumption is multiple imputation, which consists of generating multiple copies of the original dataset, each with missing values replaced by values randomly generated (Greenland & Finkle, 1995). However, multiple imputation analyses will avoid bias only if enough variables predictive of missing values are included in the imputation models. For example, socio-economic disadvantage (Bifulco et al., 2012) and parent's education (Palmer et al., 2013) have been found to be strongly predictive of experiences of childhood adversity. Unfortunately, data on these covariates were not available in the current study and therefore, it was not possible to predict missing values for the main predictor using multiple imputation analyses.

Moreover, there are circumstances in which analyses of complete cases will not lead to bias. Missing data in predictor variables are considered not to result in biased analyses of complete cases if the reasons for the missing data are unrelated to the outcome (Sterne et al., 2009). When missing values are confined to a single variable *y*, such as childhood adversity, the standard procedure is to compare the distributions of fully observed variables for respondents and non-respondents to the CECA.Q via *t* tests and chi-square tests for the differences in means and distributions (Little, 1988). Therefore, the sample is split into cases with that variable observed and cases with that variable missing. The observed values of the other variables in the two groups are then compared by two sample *t* tests or chi-square tests. Significant differences between these means are evidence that the data are not missing at random. This was done and results are presented on page 125 of Chapter 4 (Results section 4.1).

Main baseline assessment tools

An extensive battery of assessments was conducted face-to-face with participants in the baseline GAP study, taking an average of 15 hours to complete. These included diagnostic instruments, neuropsychological testing, biological measurements and psychosocial questionnaires. It is beyond the scope of this thesis to describe all of these so only the most relevant assessment tools are outlined below.

Medical Research Council Sociodemographic Schedule (Mallett, 1997).

This schedule was completed with both psychosis cases and community controls. It provides data on living circumstances, employment/education and relationship status of respondents over the preceding 5 years. For the purposes of this thesis, only the questions pertaining to the age of the respondent at the time of interview, gender, ethnicity, baseline relationship and employment status are relevant. Gender was classified as male or female.

Participants were asked to describe their ethnic origin according to the 16 categories employed by the UK Office of National Statistics (ONS) census in 2001 (www.statistics.gov.uk/census 2001). These were as follows: (i) White British; (ii) White Irish; (iii) Other White; (iv) Mixed: White and Black Caribbean; (v) Mixed: White and Black African; (vi) White and Asian; (vii) Other Mixed; (viii) Indian; (ix) Pakistani; (x) Bangladeshi; (xi) Other Asian; (xii) Black Caribbean; (xiii) Black African; (xiv) Black Other; (xv) Chinese; and (xvi) Other. For the analysis, the smallest ethnicity categories were collapsed into an 'Other' group (Mixed groups, Black Other and Other), a 'White Other' group (White Irish and White Other), and an 'Asian (all)' group (Indian, Pakistani, Bangladeshi, Chinese and Other Asian). This left six main ethnic groups: White British, White Other, Black Caribbean, Black African, Asian (all) and Other.

Participants were asked to describe their current relationship status, according to the following categories: single, married/living with someone, in a steady relationship, divorced, separated and widowed. For the ease of analysis, a dichotomous variable was created collapsing into a 'in a steady relationship' group the categories married/living with someone and in a steady relationship (coded as 0), and collapsing in a 'not in a steady relationship' group the categories single, divorced, separated and widowed (coded as 1).

Participants were asked whether they were currently employed, according to the following categories: unemployed, student, employed. In case of current employment status participant were asked if part-time or full-time employed and to indicate the position held (the latter was not collected for data entry though). For the purpose of this thesis, a dichotomous variable was created collapsing the categories part time and full time employed and student into an 'employed/student' group (coded as 0) and coding the 'unemployed' group as 1.

Nottingham Onset Schedule (NOS; Singh et al., 2005)

Information on duration of untreated psychosis (DUP) was collected using a shortened version of the Nottingham Onset Schedule (NOS; Singh et al., 2005). The NOS provides a standardised and reliable way of recording early changes in psychosis and identifying relatively precise time periods for measuring several durations in emerging psychosis (Singh et al., 2005). In line with these criteria, in this study DUP was defined as the period in weeks from the date of the first appearance of clinically relevant psychotic symptoms (approximated to a score of 4 or more on relevant items from the Positive and Negative Syndrome Scale; Kay et al., 1987), regardless of how long they persisted, to the date of first contact with mental health services for psychosis (Morgan et al., 2006; Singh et al., 2005). This was calculated based on clinical records (with some informant interviews) of each patient. The standard rules of thumb for dating recommended by the authors of the measure (Singh et al., 2005) were employed to improve reliability of the measure, namely using the actual date where known, or otherwise using the middle of the month (15th) where only the month was known, or the middle of the year (1st July) if only the year was known.

Previous studies have consistently showed that DUP is a strong predictor of both clinical and social outcomes in psychosis in terms of greater positive and negative symptom severity, lower remission rates, and greater functional impairment (Cechnicki et al, 2014; Marshall et al., 2005; Penttilä et al., 2014; Perkins et al., 2005; Tang et al., 2014; Üçok & Ergül, 2014). Recently, it has been shown that childhood maltreatment is associated with longer treatment delay (Broussard et al., 2013; Haug et al., 2015). Therefore, DUP was added as confounder to analyses testing the association between childhood adversity and one-year psychosis outcomes.

Operational Criteria (OPCRIT; McGuffin et al, 1991)

Validation of clinical diagnosis was obtained using the computerized Operational Criteria system (version 2004). All diagnoses were performed by qualified

psychologist and psychiatrists, subject to comprehensive training and achievement of good inter-rater reliability (κ=0.91). Clinical information was collected by looking at the electronic Patient Journey System (ePJS) and discharge summaries referring to the first month following first contact with mental health services for psychosis. The presence or absence of symptoms was measured by the OPCRIT checklist using the strict OPCRIT definitions. Checklist ratings were entered into the OPCRIT programs which generate diagnoses for the main categories of affective and psychotic disorders defined according to a range of major classification systems. For the purpose of this thesis broader diagnostic groups were created based on classification from the tenth edition of the International Classification of Diseases (ICD-10; World Health Organization, 1992a). Patients diagnosed as having bipolar disorder or major depression with psychotic symptoms were included in the affective psychosis group (ICD-10 codes F30-33), while patients with schizophrenia, schizophreniform disorder, schizoaffective disorder formed the non-affective psychosis group (ICD-10 codes F20-29).

Global Assessment of Functioning Scale (symptoms and disability) (GAF; Endicott et al., 1976).

The GAF is a rating scale for evaluating a person's clinical, social and occupational functioning on a hypothetical continuum of mental health to illness and ranges from 1, representing the hypothetically sickest individual, to 100, representing the hypothetically healthiest (American Psychiatric Association, 1994). The scale is divided into 10 equal parts and provides defining characteristics for each 10-point interval, though the rater needs to decide on an exact number. Two separate ratings on the GAF based on dimensions of (i) psychiatric symptoms and (ii) social and occupational function were assigned. The GAF was rated by the interviewer only for psychosis cases to ascertain the severity of their symptoms and level of social functioning over the last 7 days before baseline interview. A copy of this instrument is provided in Appendix X.

Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987*)*

The PANSS (Kay et al., 1987) was conceived as an operationalized, drug-sensitive instrument that provides balanced representation of positive and negative symptoms and measures their relationship to one another and to global psychopathology. The PANSS has 30-items each rated on a 7 point (1–7) scale; items are grouped into 3 subscales: positive symptoms (7), negative symptoms (7), and general psychopathology (16). Higher scores indicate greater severity of illness over the last 7 days before interview. Previous studies found that the three scales were shown to be normally distributed and independent of each other; they were robust to the effects of mood, chronicity, medication side-effects and cognition (Kay et al., 1987; 1988; 1989). Sub-scale total scores have been associated with a number of clinical, treatment and cognitive variables, including premorbid adjustment (Krauss et al, 1998), but not outcome. One of the strengths claimed for the PANSS is consistency in scoring individual patients over time and illness course (Mortimer, 2007). For ease of analysis, to test for the associations between childhood sexual abuse and specific psychotic symptoms, each symptom item from the PANSS was converted into a binary variable, with scores from 1 to 3 coded as 0 (from absent to mild symptoms) and scores from 4 to 7 being recoded as 1 (from moderate to extremely severe symptoms). A copy of this measure is provided in Appendix XI.

Psychosis Screening Questionnaire (PSQ; Bebbington & Nayani, 1995)

All controls completed the Psychosis Screening Questionnaire (PSQ; Bebbington & Nayani, 1995). It comprises six questions covering symptoms of hypomania, thought insertion, paranoia, strange experiences and hallucinations, along with enquiry into past treatment for a psychiatric or psychological problem (see Appendix XII). Those reporting current or previous treatment for psychosis were automatically excluded but those who had received treatment for other disorders without any psychotic features (e.g. depression) were not.

Responses to the 5 symptom questions are coded 0 (no), 1 (unsure) or 2 (yes) and the initial probes for these items are followed up with secondary questions if the response to the probe question is 'yes' or 'unsure' to establish the presence of psychosis-like experiences. Question 6 (previous treatment) is open-ended and allows for free text responses. Endorsement of one or more symptoms (hypomania, thought insertion, paranoia, strange experiences, hallucinations) using the criteria outlined by Morgan et al. (2009), that is a positive response on the PSQ to both a probe item and its supplementary questions (i.e. the more 'psychotic' experiences; Johns et al., 2004), was considered to indicate the presence of psychosis-like experiences (PLEs).

Family Interview for Genetic Studies (FIGS; NIMH Genetics Initiative, 1992)

The FIGS (https://www.nimhgenetics.org/interviews/) was used to obtain information about each participant's family history of mental health problems. This interview begins with a brief construction of a pedigree diagram for the participant's first degree relatives and a series of screening questions to elicit information about possible mental health problems in these relatives. Positive responses to any of these are followed up with more specific questions to obtain symptom and treatment information for each potentially affected relative. Only 3 of these supplementary sections were chosen for this study, namely depression, mania, and psychosis. For cases, this interview was supplemented by information retrieved from clinical records. A copy of the FIGS is provided in Appendix XIII.

To maximize this measure of proxy genetic risk, only information on first degree relatives (participant's biological mother and father, full siblings, and children) was used. The FIGS consensus diagnoses were divided into several familial risk variables. Firstly, "family psychosis" denoted the presence (1) or absence (0) of a current or previous diagnosis of psychosis in at least one first degree relative. A "family mental illness" variable referred to the presence (1) or

absence (0) of current or past psychosis, mania, or depression in at least one first degree relative. A "parental mental illness" variable was also created that indicated the presence (1) or absence (0) of a current or previous diagnosis of psychosis, mania, or depression in at least one biological parent. Similarly, a variable for "parental psychosis" was created that denoted the presence (1) or absence (0) of current or past psychosis in at least one biological parent.

DNA samples collection and storage

A blood sample was also collected from both psychosis cases and controls (two 6 mls EDTA tubes). Participants who refused venopuncture (25%) were asked to provide a DNA sample using a cheek swab kit, provided by the laboratory of the MRC Social, Genetic and Developmental Psychiatry Centre (SGDP). The DNA was extracted from both blood samples and cheek swabs, following standard procedures. All samples were bar-coded to preserve confidentiality and blindness to clinical status and appropriately stored in the SGDP -80^{o}C freezer for later analysis.

The genotyping of the genetic polymorphisms selected to test the thesis hypotheses was carried out at the SGDP laboratory by Dr Conrad Iyedgbe post-doc neuroscientist leading the genetic analyses of the GAP study. A comparison of genotype results for 360 individuals with overlapping blood and cheek swab DNA revealed there was 100% concordance between blood- and cheek-derived genotype data. The DNA was extracted using a standard phenol-chloroform extraction procedure. A Taqman SNP assay was used to genotype the *COMT* gene at the rs4680 locus, the *AKT1* gene at the rs2494732 locus and the *FKBP5* at the rs1360780 locus (kit format at http://www.appliedbiosystems.com). After an initial Taq polymerase activation/DNA denaturation step, samples were subjected to PCR reaction following standard Applied Biosystem dry DNA protocol. Amplification products were analyzed using the Applied Biosystems 7900HT Fast Real-time PCR System. Genotype calls were made based on a clustering algorithm with quality value of 95%.

Validation of self-reported ethnicity

To confirm self-report of ethnicity, genetic ancestry was derived using a panel of 57 ancestry informative genetic markers. These were genotyped using iPLEX technology developed for the MassArray platform (Sequenom Inc., San Diego, California) and an ancestry score was derived using the program Structure (Falush et al., 2003) to implement a model-based (Markov Chain Monte Carlo) clustering algorithm. Individuals who score between 96% and 100% for genetic cluster membership were used to create a three-way ancestral axis based on Black African, European Caucasian, and Asian ancestry. These reference groups were used to index genetic ancestry for the remaining sample. Eighty-nine percent of participants had information on both self-reported ethnicity and ancestry markers. The level of overall agreement between self-reported and genetic ethnicities (96%) was reassuringly high.

Quality control of genotype

With quality control, SNPs were excluded that: deviated from Hardy–Weinberg equilibrium with a P-value smaller than 1×10^{-5} in controls; had a minor allele frequency smaller than 1%; had discordant gender information; showed evidence of relatedness between individuals in the sample; and had a genotyping failure greater than 1%. Principal component analysis had been applied in EIGENSTRAT to model population structure and any outlier individuals were excluded. The principal component showing significant difference in ancestry between cases and controls was included as a covariate in the polygenic risk score analyses to control for the effects of population stratification. Population stratification refers to the differences in allele frequencies between individuals of different ancestry and can confound the association between genetic variants and disease, when ancestry differs between cases and controls (Cardon et al., 2003; Knowler et al., 1988).

Polygenic risk scores

The polygenic risk scores were constructed using the results from a large meta-analysis from the Schizophrenia Working Group of the Psychiatric Genomics Consortium (http://www.med.unc.edu/pgc/). A mega-analysis was performed between 52 ancestry matched case-control samples, including 34,341 European individuals with schizophrenia and 45,604 controls. A subset of around 9.5 million autosomal SNPs in linkage disequilibrium (LD) was selected. SNPs were pruned using the 'clumping' procedure implemented in PLINK (http://pngu.mgh.harvard.edu/purcell/plink/) which retains those SNPs most associated with schizophrenia in the discovery set from each LD block and removes SNPs in high LD showing less evidence of association (maximum r2=0.25, window=250kb, filtering for significance, PLINK-command: --clump-p1 0.5 --clump-p2 0.1 --clump-r2 0.25). Subsets of SNPs were selected from the results at five significance thresholds ($p<0.1$, $p<0.2$, $p<0.3$, $p<0.4$, $p<0.5$). Using such thresholds, the number of risk alleles possessed by each individual in the target sample was calculated, weighted by the log odds ratio from the discovery sample, and aggregated into a polygenic score (Psychiatric Genomic Consortium, 2014).

Following quality control, there were 86 White first-episode psychosis cases and 110 White unaffected controls available with both genome-wide genotype data and information on experiences of childhood adversity. In these analyses, I could only include participants of Caucasian parentage as previous testing of the polygenic score in the GAP participants with African ancestry found that it was not predictive of psychosis. The reasons for this discrepancy may be that: the polygenic score of the GAP independent sample was based on the European discovery sample from Psychiatric Genomics Consortium (Psychiatric Genomic Consortium, 2014); Africans have higher genetic diversity; limitations of the genotyping arrays used; and there could be different genetic influences on disease, as well as biological and environmental factors potentially playing a greater role in this ethnic group in the UK.

Childhood Experience of Care and Abuse Questionnaire (CECA.Q)

Information on adverse childhood experiences was obtained at baseline with the short version of Childhood Experience of Care and Abuse Questionnaire (CECA.Q; Bifulco et al., 2005). The CECA.Q was developed as a brief tool to retrospectively assess the presence and severity of a range of adverse experiences occurring prior to the age of 17 years. This measure has several advantages: it covers different areas of childhood experience; it utilises screening questions followed by more detailed supplementary probes; it is designed to elicit concrete examples of adversity; has a published coding system (Bifulco et al., 2005) to score the severity of the responses provided; decisions regarding experience of adversity are investigator-based rather than relying on the respondent's interpretation; and has published cut-points (Bifulco et al., 2005) to ensure reasonably minor instances of adversity are excluded.

The CECA.Q has also been shown to have satisfactory levels of test-retest reliability and concurrent validity (Bifulco et al., 2005; Smith et al., 2002). Moreover, the instrument has previously been used with psychosis patients and has been shown to have good inter-rater reliability, convergent validity with other assessment tools, and to be unaffected by severity of symptoms (Fisher et al., 2011).

Composition of the CECA.Q

A full copy of the questionnaire is provided in Appendix XIV. This self-report questionnaire comprises four sections, described in detail below.

Section 1: Living arrangements

This section concerns who brought the respondents up in their first 17 years. Firstly, parental arrangements are documented for the mother and father figures that the respondent physically lived with from birth until the age of 16. Each arrangement is required to have lasted for at least one year and the age at which each started is noted. These included all possible parental combinations, such as

biological mother and biological father, biological mother and no father figure, step-parents or parent's live-in partner, other relatives, adoptive or foster parents, and neither mother nor father if respondents lived alone or with friends.

Secondly, the respondent is questioned regarding any length of stay in an institution prior to 17 years of age. These include children's homes, hospitals, detention centres and boarding schools. There was no minimum limit to the length of time in the institution and each separate stay was documented along with the age that the respondent entered and left the institution.

Section 2: Parental loss

Loss of a parent through death is recorded independently of separation from a parent whilst he or she was alive. Death of the biological mother and father of the respondent before s/he is 17 years old is noted along with the age of the respondent at their death. Separation from their biological mother or father for a period of at least six months is also documented for respondents along with their age when this first occurred and the length of the separation in years. This involves not physically living with the parent for the entire period and can only occur whilst the parent is alive (if separation only occurred due to a parent's death then this was entered only under the loss item). Where separation was indicated, the respondent was asked the reason for this. For instance, parent's decided to separate or divorce, the parent was too ill to stay at home, they resided elsewhere due to work commitments, or the parent abandoned the respondent.

Section 3: Physical abuse

In the CECA.Q physical abuse is defined as repeated exposure to physical violence from any mother or father figures before 17 years of age. Mild forms of punishment such as being smacked or hit with a slipper are excluded. This section begins with a screening question: "*When you were a child or teenager*

were you ever hit repeatedly with an implement (such as a belt or stick) or punched, kicked or burnt by someone in the household?". Positive responses are followed up with more detailed questions concerning the frequency and age of occurrence, method of hitting, nature of injuries sustained and the state of mind of the perpetrator at the time. These supplementary questions are completed for the relevant mother and father figure separately. If multiple mother or father figures physically abused the respondent then the most severe instances are selected. At the end of this section, respondents are also asked whether anyone else in the household was violent towards them. This information was noted but not included in the calculations for parental physical abuse.

Section 4: Sexual abuse

Sexual abuse is considered to be any sexual experience prior to age 17 years with (i) an adult or (ii) unwillingly with a peer. These experiences are not limited to the immediate family. Exposure by a stranger without any physical contact and consensual sexual contact with peers is excluded. This section begins with three compulsory screening questions that attempt to elicit sexually abusive experiences before 17 years of age by asking the same question in slightly different ways: a) "*When you were a child or teenager did you ever have any unwanted sexual experiences?*"; b) "*Did anyone force you or persuade you to have sexual intercourse against your wishes before age 17?*"; c) "*Can you remember any upsetting sexual experiences before age 17 with a related adult or someone in authority e.g. a teacher?*". A 'yes' or 'unsure' answer to at least one of these questions is followed up with more detailed questions on the relationship with the perpetrator, frequency and age of occurrence, and the nature of the exposure (degree of contact). These supplementary questions are completed for the earliest experience of sexual abuse and then one subsequent experience. If multiple subsequent experiences are reported then the second documented incident is the most severe of these experiences or if they are all of the same degree of severity then the one occurring at the earliest age is chosen.

Administration and scoring of the CECA.Q

The guidelines proposed by Arksey and Knigh (1999) and Kitson et al. (1996) for conducting interviews on sensitive topics were followed. This questionnaire was read out to all participants to improve the accuracy of the fixed category responses obtained by seeking clarification where answers were ambiguous and explaining questions where the respondent indicated s/he did not understand. The scoring of this data was conducted in accordance with the guidelines published by Bifulco et al. (2005). The most conservative cut-points for each form of abuse (sexual, physical) were selected in order to ensure that only severe instances were counted as 'abusive' and the possibility of including false positives was minimized (Bifulco et al., 2005). No attempt was made to fill in gaps in the data. Where items were missing the relevant variable was not computed for that individual.

Family arrangements

The total number of parental arrangements before 17 years of age (each lasting at least a year) was counted up. A dichotomous variable was created by coding those with 1 or 2 arrangements as 0 (no/minimal disruption) and those with 3 or more arrangements as 1 (disrupted living arrangements). This variable was intended to be a proxy for family chaos by capturing individuals who had experienced multiple care arrangements.

Institutional care

Given that most of the existing literature has focused on the detrimental effects of children being removed from their families and placed in institutions (e.g., Bebbington et al., 2004; Carter et al., 2002) rather than on separations involving boarding schools or short-term hospital treatment, only the former type of institutional care was considered in this study. Hence, individuals who reported being placed in local authority care for any length of time were rated as 1 (taken into care) whilst those who reported no institutional care or being in other forms of institutions were coded as 0 (no care).

Parental death

The death of the biological mother or father prior to the respondent reaching 17 years of age was coded for each parent separately into 1 (loss) and 0 (no loss) and an overall variable of any parental loss (either mother or father died) was used in this thesis.

Parental separation

Similarly, reports of separation from the biological mother or father prior to 17 years of age was coded for each parent separately into 1 (separation) if this lasted for at least six months and 0 (no separation) if no separation was reported or it lasted for less than six months. Again an overall variable of any parental separation (separated from either mother or father) was used in this thesis.

Parental physical abuse

All respondents who answered 'no' to the screening question for physical abuse were automatically given a score of '0'. In those who screened positive for physical abuse, separate scores for maternal and paternal physical abuse were obtained by adding together the relevant responses for the following items: 6.21c – more than once (1), only once (0); 6.21d/e - hit with a belt/stick or punched/kicked (1), hit with hand/other (0); 6.21f - resulted in injury/bruising (1), no injuries (0); and 6.21g - perpetrator out of control (1), in control (0). This resulted in scores ranging from 0 to 4 for each parental figure. In order to create one dichotomised physical abuse variable, maternal and paternal scores of 0-2 were recoded as 0 (no/non-severe physical abuse) and scores of 3 or 4 were coded as 1 (severe physical abuse) consistent with the published cut-off point (Bifulco et al., 2005).

Sexual abuse

All respondents who answered 'no' to all three screening questions for sexual abuse were automatically given a score of '0'. A total score for the first unwanted sexual experience was calculated by adding together the responses for the following items: 6.22d ii -perpetrator known (1), not known (0); iii - perpetrator relative (1), not relative (0); iv – more than once (1), only once (0); v - perpetrator touched child's private parts (1), didn't involve this (0); vi – sexual intercourse (1), not sexual intercourse (0). The possible range of scores for sexual abuse was therefore 0 to 5. This procedure was repeated for the second unwanted sexual experience. In order to create a dichotomised sexual abuse variable, firstly scores of 0 or 1 for each sexual abuse experience were recoded as 0 (no/non-severe sexual abuse) and scores of 2-5 were coded as 1 (severe sexual abuse) consistent with the published cut-off point (Bifulco et al., 2005). A rating of 1 for either the 1st or 2nd sexual abuse dichotomised variables (or both) was deemed to indicate presence of 'any sexual abuse' and coded as 1 (severe sexual abuse) whilst ratings of 0 for both experiences were coded as 0 (no/non-severe sexual abuse).

Number of childhood adversities

A composite variable was also computed to summarise how many of the different adversities had been experienced by each individual. This 'total adversity' score involved summing the dichotomous CECA.Q subscale scores (range 0-6) and then recoding the total into an ordinal scale of 0 (none), 1 (single adverse experience), and 2 (multiple adverse experiences).

One year follow-up assessment measures

All of the following measures were completed by a researcher retrospectively from electronic mental health records that clinicians had entered prospectively. The one-year follow-up period was taken as the date of first contact with mental health services of the South London and Maudsley Mental Health NHS

Foundation Trust (SLAM) for psychosis to the date exactly one year later. If records were not available on ePJS, information on deaths and emigrations occurring over the one-year period from first contact with mental health services were identified by a case-tracing procedure with the Office for National Statistics (ONS) for United Kingdom using name, sex, date of birth and last known address.

The Follow-up Psychiatric and Personal History Schedule (FU–PPHS; Sartorious et al., 1986).

The FU-PPHS is a schedule to record information about the mental state, general behavior, events and personal history of the patient during a follow-up period (for this thesis this was over the first year since contact with mental health services for psychosis). The sections of the instruments are arranged in the format of a life-chart. A brief narrative note should be made throughout the follow-up period, summarizing the symptoms, general behavior and any relevant happenings. The FU-PPHS is structured in 10 sections containing: patient's demographic details and starting and finishing time of the follow-up (Section 1); the patient's psychiatric history, including present illness and past episodes, onset, progression of symptoms, and treatment (Section 2); medical history (Section 3); living arrangements (Section 4); household, family and marital status (Section 5); livelihood and occupation (Section 6); education (Section 7); religion (Section 8); social network and social behavior (Section 9); and a last section containing details of the patient if s/he died during the follow-up period (Section 10). A copy of sections of the instrument relevant for this study is provided in Appendix XV.

The FU-PPHS, previously used in World Health Organization multi-centre studies of the incidence and outcome of schizophrenia (Jablensky et al, 1992) and in previous studies of pathways to care (Burnett et al, 1999), has shown good validity and reliability (Jablensky et al, 1992). For the purpose of this study, FU-PPHS was completed using clinical records through the Electronic Patient

Journey System (EPJS) for the year following first contact with mental health services for psychosis. Inter-rater reliability was established between 3 trained researchers on 10 cases. Cohen's κ and intra-class correlation values indicated robust agreement among the raters (range: 0.992-1.000). Efforts were made to maintain inter-rater reliability across the entire follow-up, including careful calibration and standardization procedures and regular, in-depth review of a sample of assessments. Raters were blind to diagnostic information from previous baseline assessments.

Extensive information was collated across three course and outcome domains (clinical, social and service use) from clinical records. Patients were followed up a mean of 11.3 months (SD=2.23) after first contact with mental health services for psychosis. A detailed flow chart of one-year follow-up attrition rate is provided in Chapter 4 (Results section 4.2).

I extracted data on the outcomes of psychosis from the following sections of the FU-PPHS for use in this thesis:

Section 2: Mental state and treatment

Number of days in institution

This item includes inpatient treatment in a psychiatric hospital or any other institution to which the patient has been admitted because of mental disorder. Hospitalizations unrelated to mental disorder are not included. The total number of days spent in an institution throughout the year for psychosis following the first contact with mental health services was counted up (range 0 to 365 days). As the number of admission days was non-normally distributed, with skewness of 1.71 (SE = 0.16) and kurtosis of 3.42 (SE = 0.32), the number of days that patients spent on a psychiatric ward was dichotomised at the median into less than 49 days versus 49 days or more.

Compliance with drug treatment

This section assesses the extent to which the patient has followed the instructions given to him with regards to the prescribed treatment, especially as concerns regularity of intake and dosage. A code of 0 is given when drugs are taken regularly and in adequate dosage; a code of 1 corresponds to drugs taken irregularly (with lapses for at least 3 days occurring more than once) or in an inadequate dosage; 2 is coded when drugs prescribed are probably not taken at all. Codes of 8 and 9 are attributed when no drug treatment has been prescribed throughout the follow-up period or information is not available, respectively. In order to create a dichotomized compliance with drug treatment variable, firstly score of 0 was maintained as 0 (patient compliant with drug treatment) and scores of 1-2 were coded as 1 (patient not compliant with drug treatment). Scores of 8 and 9 were recoded as -99 (information missing or not applicable).

Remission

FU-PPHS defines remission as a state following a psychotic episode, in which none of the symptoms listed as characteristics of a psychotic episode are present (a definition of psychotic episode according to PPHS criteria is provided below, see the item on pattern of course). During a remission a patient may exhibit a variety of non-psychotic symptoms (e.g. depressed mood, neurotic manifestations) or some of the so called negative symptoms, or be entirely symptom free (incomplete or complete remission, respectively). A rating of remission (as well as a rating of a psychotic episode) should be based only on ascertainable absence (or presence) of psychotic symptoms and not on whether the patient is taking any psychotropic medication or not, or whether he is hospitalized or not. The absence of psychotic symptomatology would qualify as a remission only if it lasts for 30 days or more. This section starts with the question: *"a) Has the patient had a remission of psychotic symptoms for a period of at least 30 days since the initial evaluation?".* In case of affirmative response this is followed by: "*b) for how many weeks was the patient in the episode of*

inclusion – i.e., the number of weeks from the first onset of psychotic symptoms until the beginning of the patient's first remission". A dichotomized remission variable was created: a code of 0 was attributed if the patient had no remission of psychotic symptoms for a minimum of 30 days since first contact with mental health services for psychosis and a code of 1 was attributed in the case of symptomatic remission for at least 30 days over the follow-up period.

Pattern of illness course

This section assesses the course of the patient's psychotic illness since the first contact with psychiatric services, from a condition of complete or nearly complete recovery without relapses or exacerbations of psychotic symptoms to a condition of continuous psychotic illness. The FU-PPHS provides in its Appendix an operational definition of a psychotic episode, central for the assessment of course and outcome of the illness. A psychotic episode is characterized by the presence of at least one of the following symptoms:

(i) Hallucinations or pseudo hallucinations
(ii) Delusions
(iii) Marked thought and speech disorder other than simple retardation or acceleration
(iv) Qualitative (e.g. catatonic) psychomotor disorder, other than simple retardation or acceleration
(v) Emergence or marked exacerbation of bizarre and grossly inappropriate behavior strongly suggestive of the presence of hallucinations or delusions (e.g. talking or giggling to self)

Or, in the absence of the manifest symptoms listed above a psychotic episode may be considered as present if at least two of the following symptoms have emerged or become markedly exacerbated:

(a) Severe loss of interests, initiative and drive leading to a serious deterioration of performance of usual activities and tasks

(b) Emergence or marked exacerbation of social withdrawal

(c) Severe excitement, destructiveness or aggression

(d) States of overwhelming fear

(e) Gross and persistent self-neglect

Furthermore, in order to be considered as a psychotic episode, the above symptomatology must be preceded or followed by a period of at least 30 days during which the symptoms were absent (as defined by remission).

Clinical records are examined in order to identify the pattern of illness course which best described the patient's condition since the initial evaluation. A code of 0 is given in the case of a complete or nearly complete recovery without relapses or exacerbations of psychotic symptoms; 1 is coded in the case of no relapses or exacerbations of psychotic symptoms but with residual personality change; a code of 2 in the case of one or more relapses with no marked personality change; 3 in the case of one or more relapses with personality change and a code of 4 in the case of continuous illness. For the analysis conducted in this study, a categorical variable was created: firstly scores of 0 or 1 were recoded as 0 (recovery/no relapses), scores of 2-3 were coded as 1 (one or more relapses of psychotic symptoms) and score of 4 was recoded as 2 (continuous illness).

Section 5: Marriage, household and family

Marital status

This item rates any change in the patient's marital status since the index episode examination. A code of 0 is given if no changes in the patient's marital status occurred; 1 in case of marriage; 2 for engagement or marriage arranged for a future date; 3 represents broken engagement or marriage arrangement; 4 divorced; 5 separated; 6 widowed; 7 other marital status changes and a score of

8 in the case of more than one change listed above. A dichotomized relationship status variable was created attributing a code of 0 if the patient was married or in a steady relationship at the time of follow-up or 1 if the patient was single, divorced or widowed at follow-up.

Section 6: Livelihood/Occupation

Current employment status (last 30 days)

This section starts with the question: *"Has the patient been employed at a paid job (i.e. an earning occupation) in the last 30 days?"*. A code of 0 is given in case of unemployment and 1 if the patient has been employed in the last 30 days. If the patient has not had a paying job in the last 30 days, the reasons for unemployment are rated (Section 6.2). These include: being a student, housewife, worker in unpaid family concern (e.g. family farm), the patient's mental illness (e.g. hospitalization or refusal to work), physical disability or illness or general employment situation. A dichotomized binary current employment variable was created for this thesis to rate the employment status at the one-year follow-up point: a code of 0 was attributed if the patient was employed or was involved in a study program in the last 30 days of follow-up and a code of 1 was assigned in the case of unemployment.

Global Assessment of Functioning Scale (GAF; Endicott et al., 1976)

The GAF (Symptoms and Disability) was completed from clinical records through the Electronic Patient Journey System (EPJS) for the 7 days prior to the one-year anniversary of first contact with mental health services. Researchers involved in rating GAF via notes completed intensive reliability checks (Cronbach alpha ~0.90). The same raters were involved in the GAF and FU-PPHS record-based assessment to assist reliability. Furthermore, comparing GAF ratings via notes with GAF ratings via interview conducted one year from first contact with psychiatric services for a subsample not included in this study (n=93), also

showed a good consistency for both symptoms and disability scales (intra-class correlation range: 0.974-1.000, all p's<0.001).

Analytic approach

All the data collected, including the genotyping results, were recorded in SPSS version 21 and analysed using Stata 11 (StataCorp, 2009). A power calculation using the program QUANTO Version 1.2.4 software (http://hydra.usc.edu/gxe/) indicated over 90% statistical power (0.92) at a significance level of 0.05, 2-sided, for unmatched case–control analyses to obtain an OR of 2.0 with the total sample size in this study, based on estimates of exposure to childhood adversity amongst the UK general population (25%; Radford et al., 2011).

Chi-square tests and t-tests were used to test for associations between the potential confounding variables and presence of psychotic disorder and to establish if missing data were likely to bias the results. Baseline analyses were adjusted for the following potentially confounding factors (where relevant): sex (male or female), age (18-65), ethnicity (White British, White Other, Black Caribbean, Black African, Asian [all] or Other), and level of education (no qualification, GCSE/O levels, A levels/vocational/college, or University/Professional Qualifications). Unfortunately IQ data was not available on a large enough number of participants to be included as a confounder. Additionally, no data was available on the socio-economic status of the participants and thus this could not be included as a confounder either. Follow-up analyses were adjusted for baseline clinical and social/vocational functioning (e.g. duration of untreated psychosis, GAF-symptoms and disability scores, relationship and employment status, compliance with medications).

For the GxE interaction analyses, I adopted a model focused on interaction as departure from additivity rather than departure from multiplicativity (Knol et al., 2007). As discussed in Chapter 2, when biologic interaction is examined, assuming that two factors are both needed to cause disease, we should focus on interaction on an additive scale (Rothman, 2002). On

the assumption that the combined effect of A and B is larger, or smaller, than the sum of the individual effects of A and B, presence of synergy between genetic risk and childhood adversity was indicated by positive deviations from additivity.

A reasonably liberal approach was taken to *P* values with <0.20 considered indicative of a trend, <0.10 taken as evidence of a trend, <0.05 seen as conventionally significant, and <0.01 as highly significant. This was to ensure that no potential effects were missed, particularly in relation to the interaction analysis.

A complete and detailed description of the statistical analyses conducted in the Results Chapters (4-7) is provided below.

Chapter 4

Binary logistic regression was used to analyse the relationship between each form of adversity and case-control status while controlling for potential confounders. This was done firstly with the sample unstratified, and then stratified by (i) gender and (ii) ethnicity, with likelihood ratio tests used to determine interaction effects.

A factor analysis (FA) using the principal-component factors method with Promax rotation was conducted on the 30 PANSS items to reduce them to factors representative of psychotic symptoms. Factors resulting from FA can be thought of as underlying constructs responsible for producing the variable scores, assuming a theory development at its base (Tabachnick et al., 2001). Promax rotation was selected for this analysis, as I hypothesized that clusters of psychotic symptoms might be correlated with each other. Cronbach's alpha was used to assess reliability for each of the extracted factors. Finally, mean values for each factor were computed by averaging the values for the PANSS items that loaded on each factor ($\lambda \geq 0.4$). Linear regression was used to test for the association between types of childhood adversity and psychosis dimensions.

Binary logistic regressions were also used to analyse the relationship between each form of adversity and dichotomous follow-up variables

(symptomatic remission, length of hospital admission, compliance with medications, relationship and employment status at one-year follow-up). Ordered logistic regressions and linear regressions were used for ordinal (illness course) and continuous follow-up outcome variables (GAF-symptoms and disability scores at one year) respectively.

Chapter 5

First, main effects of each type of childhood adversity and (general and psychotic) family mental illness on psychosis caseness were assessed using a series of binary logistic regressions. Second, I tested whether differences in an individual's proxy genetic liability might drive differential environmental exposure. Specifically, the passive type of gene-environment correlation (rGE) was explored using binary logistic regression analysis to estimate odds ratios (OR) of the associations between history of parental mental illness or parental psychosis and (1) psychotic disorder in the participants, and (2) each subtype of childhood adversity. If parental liability is associated with both disorder and adversity then this indicates the possibility of a passive rGE (albeit a 'proxy gene' by environment correlation). The possibility that parental psychopathology may attenuate the association between childhood adversity and psychosis was also addressed by rerunning the association between childhood adversity and psychotic disorder with parental history of psychosis added as a confounder.

Next, I examined whether there was evidence that childhood adversity combined synergistically with each type of familial liability by testing for interaction on an additive scale using interaction contrast ratios (ICRs; Knol et al., 2007; Schwartz & Susser, 2006). This approach uses ORs to estimate the relative excess risk due to interaction. Biological synergism (the odds of psychosis among individuals with both risk factors being greater than the sum of the independent effects of each risk factor), is considered to be best estimated from additive statistical interaction than multiplicative statistical interaction (Morgan et al., 2014b; 2014c). As the numbers of cases and controls with a family history of

psychosis were very small, interaction analyses were only conducted for family and parental history of mental illness (psychosis, depression or mania). ICRs were used to test additive interactions when the outcome variable was dichotomous; for continuous outcomes, I used linear regression including the interaction term in the model. In linear regression, the regression coefficient of the product term reflects interaction as departure from additivity, while in logistic regression it refers to interaction as departure from multiplicativity (Knol et al., 2007), hence the use of ICRs to test for additive interactions when outcomes were binary rather than inclusion of interaction terms in the logistic regression models.

Chapter 6

The CECA.Q items relating to death of mother or father, separation from mother and/or father and total number of childhood adversities, were used, as they showed significant association with psychosis. For *COMT Val158Met* polymorphism, the number of *Val* alleles and genotypes were coded as 0 (no *Val* alleles, *Met/Met* genotype), 1 (one *Val* allele, *Val/Met* genotype) and 2 (two *Val* alleles, *Val/Val* genotype). The *AKT1* gene (rs2494732) was coded as 0 (no risk alleles, *TT* genotype), 1 (one risk allele, *C/T* genotype) and 2 (two risk alleles, *C/C* genotype). The *FKBP5* gene at the rs1360780 locus was coded as 0 (no risk alleles, *C/C* genotype), 1 (one risk allele, *C/T* genotype) and 2 (two risk alleles, *T/T* genotype).

On the assumption that each participant could carry from 0 to 6 (COMT *Val/Val*, AKT1 *C/C*, FKBP5 *T/T*) risk alleles for the three chosen candidate genes, I used the available genotyping data to obtain a "risk-alleles count". I calculated on 227/285 FEP and 185/256 controls with genetic data, an "oligogenic risk score" for *COMT*, *AKT1*, *FKBP5* genes by summing the subject's number of risk alleles across the three genes (up to six risk alleles). In addition, because of the low frequency of some of the allele counts, I collapsed them into 3 main groups (0 to 2), with 0 representing a 'low risk score' (up to two risk alleles), 1 a 'medium risk score' (3 risk alleles), 2 a 'high risk score' (4 or more risk alleles).

Binary logistic regression analysis was employed to test for associations between the different childhood adversity variables and psychosis case status. The 'genhw' command in STATA (Cleves, 1999) was used to test for Hardy-Weinberg Equilibrium (HWE; Hardy, 1908; Weinberg, 1908) in the distribution of the *COMT*, *AKT1* and *FKBP5* genotypes for cases and controls separately. In keeping with the recommendations of Sasieni (1997) the genetic data were only analysed by genotype or number of risk alleles (0, 1 or 2) rather than by total frequency of alleles as this procedure is more robust against deviations from HWE and codominance between alleles. Cuzick's (1985) non-parametric test of trend for ranks across ordered groups was performed using the 'nptrend' command in STATA to assess associations with psychosis and childhood adversity across the three *COMT*, *AKT1* and *FKBP5* genotypes. This test is considered more sensitive to trends across three or more categories than the standard chi-square test and is also robust to deviations from HWE (Cuzick, 1985). The results of this trend test were used to assess the presence of gene-environment correlation between *COMT*, *AKT1* and *FKBP5* genotype and childhood adversity in cases and controls.

Firstly, the main effects and interaction between childhood adversity and 'oligogenic risk score' was tested using a generalized linear model with the binomial distribution and identity link function specified (Wacholder, 1986) to estimate risk differences (RD) and 95% confidence intervals (CI). The main effects and interaction between childhood adversity and *COMT*, *AKT1* and *FKBP5* genotypes on the presence/absence of psychosis and on one-year outcomes was then examined separately. All analyses were adjusted for proportion of black ancestry. I tested for interaction with an additive genetic model and, if significant, dominant and recessive models were also tested. These analyses were repeated for the follow-up outcome variables which were found to be robustly associated with childhood adversity.

Chapter 7

The association between the polygenic risk score (PRS) and the presence or absence of (i) psychotic disorder and (ii) childhood adversity (i.e. gene–environment correlation) was tested using logistic regression, controlling for population stratification, sex, age and education level, because such factors could potentially bias tests for interaction. This analysis was performed separately for cases and controls in order to test if the PRS were also associated with childhood adversity in this sample.

Subsequently, examination of moderation of the childhood adversity-psychosis association by the PRS was performed with analyses of risk difference (RD) to test for interaction as departure from additivity. In line with Chapters 5 and 6, I adopted an additive interaction model because departure from additivity seems to be more in line with biological interaction (Knol et al., 2007). A generalized linear model with the binomial distribution and identity link function specified (Wacholder, 1986) was used to obtain estimates risk difference with caseness (case-control status) as the dependent variable and polygenic risk and childhood adversity, as well as their interaction, as the independent variables. Interaction analyses were also corrected for age, gender, level of education and one principal component to take population stratification into account. Effects were considered significant when p values were <0.05 or when RD 95% confidence intervals did not contain zero.

However, due to the small number of cases with both follow-up and polygenic score data available (n= 71), correlation and interaction analyses could not be performed on one-year outcomes.

CHAPTER 4 - Association of childhood adversity with presence of psychosis and with one-year outcomes

Aims of this chapter

In this chapter I sought to investigate the associations between various forms of childhood adversity with occurrence and course of psychotic disorders using baseline and follow-up data from the GAP case-control study. The specific aims are as follows:

1. To determine which adverse childhood experiences are more common amongst cases with psychotic disorders than unaffected controls.
    - Explore the association between type of childhood adversity and presence of a psychotic disorder by gender and ethnic group.
    - Explore the association between type of childhood adversity and (i) different diagnoses of psychosis, (ii) various psychosis symptom dimensions, and (iii) psychotic-like experiences amongst the controls.

2. To investigate if childhood adversity has an effect on the clinical and functional outcomes of psychotic disorders during the first year of mental health care.

3. To explore if childhood adversity has a dose-response effect on psychosis onset and one year outcomes.

Results section 4.1

Childhood adversity and psychosis

Childhood adversity and psychosis onset

A total of 431 first-episode psychosis cases and 383 unaffected controls were successfully recruited to the case-control arm of the GAP study. Of these, 285 cases and 256 controls completed the CECA.Q and were included in the following analyses. Those who completed the CECA.Q did not differ significantly from those who did not in terms of gender (cases: χ^2=3.757, p=0.055; controls: χ^2=0.658, p=0.445), but controls who completed the questionnaire were more often of non-White ethnicity (controls: χ^2=8.119, p=0.017 cases: χ^2=1.368, p=0.500) and significantly younger than the rest of the GAP sample (controls: mean age 29 vs. 32.8 years, t=3.183, p=0.002; cases: t=-1.705, p=0.089). However, in practice this was only an average of 4 years difference in age which should not have had a significant impact on memory of past events. There was also no difference in diagnostic grouping between those cases included and not included in the sample for this thesis (χ^2=11.804, p=0.378). The basic demographic data by case and control status for those included in the analyses are presented in Table 4.1.

Table 4.1 Basic demographic characteristics of psychosis cases and controls

Demographic variable	Cases (*N*=285) *n* (%)	Controls (*N*=256) *n* (%)	X^2	df	p value
Gender			2.57	1	0.065
Men	172 (60.4)	137 (53.5)			
Women	113 (39.6)	119 (46.5)			
Ethnicity			**32.60**	**5**	**<0.001**
White British	72 (25.3)	102 (39.8)			
Black Caribbean	56 (19.6)	39 (15.2)			
Black African	65 (22.8)	32 (12.5)			
White Other	30 (10.5)	50 (19.5)			
Asian (all)	24 (8.4)	16 (6.3)			
Other	38 (13.3)	17 (6.6)			
Level of education			**76.73**	**4**	**<0.001**
No qualification	48 (17.6)	7 (3.0)			
GCSE/O level	64 (23.5)	23 (10.0)			
A level	40 (14.7)	53 (22.9)			
Vocational/College	66 (24.3)	37 (16.0)			
University or professional qualifications	54 (19.9)	111 (48.1)			
Age in years			t=0.342	536	0.733
Mean (S.D.)	28.9 (9.3)	29.2 (9.9)			

df, Degrees of freedom; S.D., standard deviation. Figures in bold indicate $p<0.05$.

Compared with controls, and in line with what would be expected, cases had a lower level of education (p<0.001), and were more often of non-White ethnicity (p<0.001). There was no significant difference between psychosis cases and controls in terms of gender (p=0.065) and age (p=0.733). These variables were controlled for in the final adjusted model, where applicable.

Amongst the 285 psychosis cases included in this analysis, there were 150 (68.8%) with a non-affective form of psychotic disorder and 42 (19.3%) with an affective psychosis. I was able to calculate the duration of untreated psychosis (DUP) for 175 (61.4%) of the 285 cases and they had a mean DUP of 6.8 weeks (SD 11.02, median 2.0, range 0-52 weeks). Thus the number of cases reduces quite substantially when including this variable in analyses. I found no difference in the mean (p=0.440) and median (p=0.952) lengths of DUP, estimated as number of weeks of untreated psychosis, between first-episode psychosis patients who reported childhood adversity and those who did not.

The prevalence of each type of childhood adversity for psychosis cases and unaffected controls is provided in Table 4.2 along with the unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CI) for association with case status.

Table 4.2 Prevalence of different types of childhood adversity by psychosis case and control status

Type of childhood adversity	**Cases *n/N* (%)**	**Controls *n/N* (%)**	**Unadjusted OR**	**95% CI**	***P***	**Adjusted OR***	**95% CI**	***P***
Parental separation								
No	123/283 (43.5)	164/255 (64.3)	1.0	-	-	-	-	-
Yes	160/283 (56.5)	91/255 (35.7)	**2.34**	1.66-3.32	**<0.001**	**2.19**	1.51-3.19	**<0.001**
Parental loss								
No	248/281 (88.3)	239/255 (93.7)	1.0	-	-	-	-	-
Yes	33/281 (11.7)	16/255 (6.3)	**1.99**	1.07-3.71	**0.031**	**2.04**	1.04-4.01	**0.039**
Physical abuse								
No	220/285 (77.2)	215/254 (84.7)	1.0	-	-	-	-	-
Yes	65/285 (22.8)	39/254 (15.3)	**1.63**	1.05-2.53	**0.029**	1.35	0.84-2.18	0.217
Sexual abuse								
No	244/285 (85.6)	226/254 (89.0)	1.0	-	-	-	-	-
Yes	41/285 (14.4)	28/254 (11.0)	1.36	0.81-2.27	0.245	1.53	0.87-2.68	0.137
Institutional care								
No	271/285 (95.1)	251/256 (98.0)	1.0	-	-	-	-	-
Yes	14/285 (4.9)	5/256 (2.0)	2.59	0.92-7.30	0.071	2.33	0.79-6.82	0.123

Type of childhood adversity	Cases *n/N* (%)	Controls *n/N* (%)	Unadjusted OR	95% CI	*P*	Adjusted OR*	95% CI	*P*
Family arrangements								
Up to 2	215/271 (79.3)	184/215 (85.6)	1.0	-	-	-	-	-
3 or more	56/271 (20.7)	31/215 (14.4)	1.56	0.96-2.50	0.076	1.46	0.87-2.44	0.153
Total adversity								
0	82/285 (28.8)	130/256 (50.8)	1.0	-	-	-	-	-
1	121/285 (42.4)	81/256 (31.6)	**2.37**	1.60-3.51	**<0.001**	**2.01**	1.30-3.11	**0.002**
2 or more	82/285 (28.8)	45/256 (17.6)	**2.88**	1.83-4.56	**<0.001**	**2.17**	1.31-3.61	**0.003**

*Adjusted for gender, age at interview, ethnicity and level of education. CI, confidence interval. OR, odds ratio.

The most prevalent forms of adversity prior to the age of 17 years amongst both psychosis cases and unaffected controls were separation from father or mother for at least six months. A total of 98 (34.5%) cases and 36 (14.1%) of controls reported separation from mother; 139 cases (49.1%) and 83 (32.5%) controls reported being separated from father and a total of 81 (28.5%) cases and 27 (10.6%) controls reported separation from both parents for at least six months prior to the age of 17 years. For the 48% of cases and 63% of controls parental separation was due to parents' divorce. For the remaining cases and controls parental separation was due to a variety of reasons, such as mother or father's illness, work, mother or father abandoning the child.

All types of adversity were reported most often by cases compared to controls. A total of 13 (4.6%) cases and 4 (1.6%) of controls experienced the death of mother; 26 cases (9.2%) and 13 (5.1%) controls reported the loss of father and 6 (2.1%) cases and 1 (0.4%) control experienced the death of both parents prior to the age of 17 years. In terms of physical abuse, 43 (15.1%) cases and 21 (8.3%) controls reported that the abuse was perpetrated by the father, while 37 (13.0%) cases and 24 (9.4%) of controls reported being physically abused by the mother. Very few participants in this sample reported being taken into care during childhood.

Psychosis cases were more than two times more likely than controls to report experiences of parental separation during childhood ($p<0.001$) and approximately two times more likely to report experiences of death of a parent ($p=0.031$) or severe physical abuse by a mother or father figure ($p=0.029$). Childhood sexual abuse was marginally more common in cases than controls but this failed to reach statistical significance ($p=0.245$). Reports of being taken into institutional care were approximately twice as common amongst psychosis patients as controls, although these remained associated only at a trend level ($p=0.071$). Similarly, having more than three family arrangements was associated with psychosis caseness though only at a trend level ($p=0.076$).

In the model adjusted for age, gender, ethnicity and level of education, associations with psychosis case status remained statistically significant for parental separation and parental death. Specifically, separation from father or mother for at least six months had a two-fold higher prevalence amongst cases compared to controls ($p<0.001$), followed by loss of either parent ($p=0.039$). The association between reported sexual abuse and caseness increased slightly and reached a non-significant trend ($p=0.137$) in the adjusted analysis. The association between institutional care and psychosis case status was slightly attenuated, along with disrupted family arrangements, though both associations remained as non-significant trends ($p=0.123$ and $p=0.153$ respectively). However, in the adjusted model, the size of the association between physical abuse and psychosis case status decreased and became non-significant in the adjusted model ($p=0.217$).

Correlation matrices of types of childhood adversities show significant correlations for both cases and controls (see Appendix XVI). Therefore, significant associations between childhood adversity and psychosis were controlled for other possible adversities. The association with psychosis held for parental separation (OR=2.44, 95% CI 1.60-3.73, $p<0.001$) but it fell short of statistical significance for parental loss (OR=1.98, 95% CI 0.72-5.46, $p=0.187$). The latter result could potentially be explained by the very small number of cases ($n=11$) and controls ($n=6$) reporting parental loss without any other adversities included in the analyses.

The association with psychosis was stronger for participants who reported multiple (OR=2.89, 95% CI 1.83-4.56, $p<0.001$) than single (OR=2.37, 95% CI 1.60-3.51, $p<0.001$) adverse childhood experiences. A score test for trend provided, in fact, evidence for a linear trend ($z=4.97$, $p<0.001$) indicating a dose-response effect for repeated adverse experiences.

Association between childhood adversity and psychosis modified by gender

Reports of each type of childhood adversity for psychosis cases and controls are shown stratified by gender in Table 4.3, along with the unadjusted and adjusted odds ratios for association with case status and the results of likelihood ratio tests conducted to assess presence of an interaction with gender.

Table 4.3 Prevalence of childhood adversity amongst psychosis cases and controls by gender

Gender	Patients *n/N* (%)	Controls *n/N* (%)	Unadjusted OR	95% CI	*p* value	Adjusted[a] OR	95% CI	*p* value
Parental separation								
Men	103/171 (60.2)	45/136 (33.1)	**3.06**	1.91-4.90	**<0.001**	**2.19**	1.28-3.77	**0.004**
Women	57/112 (50.9)	46/119 (38.7)	1.64	0.97-2.77	0.062	1.46	0.83-2.56	0.188
				LR X^2=2.90, p=0.089			Adjusted LR X^2=1.60, p=0.206	
Parental loss								
Men	15/169 (8.9)	6/136 (4.4)	2.11	0.80-5.60	0.133	2.27	0.75-6.86	0.146
Women	18/112 (16.1)	10/119 (8.4)	2.09	0.92-4.74	0.079	1.63	0.67-3.96	0.283
				LR X^2=0.00, p=0.996			Adjusted LR X^2=0.25, p=0.620	
Physical abuse								
Men	49/172 (28.5)	20/137 (14.7)	**2.33**	1.31-4.16	**0.004**	1.82	0.97-3.42	0.062
Women	16/113 (14.2)	19/117 (16.2)	0.85	0.41-1.75	0.661	0.72	0.31-1.63	0.427
				LR X^2=**4.54**, p=**0.033**			Adjusted LR X^2=2.76, p=0.097	
Sexual abuse								
Men	20/172 (11.6)	9/137 (6.6)	1.87	0.82-4.25	0.135	**3.14**	1.17-8.41	**0.023**
Women	21/113 (18.6)	19/117 (16.2)	1.18	0.59-2.33	0.282	1.01	0.49-2.12	0.959
				LR X^2=1.11, p=0.292			Adjusted LR X^2=3.31, p=0.069	

Gender	Patients *n/N* (%)	Controls *n/N* (%)	Unadjusted OR	95% CI	*p* value	Adjusted[a] OR	95% CI	*p* value
Institutional care								
Men	8/172 (4.6)	2/137 (1.5)	3.29	0.69-15.77	0.136	2.36	0.44-12.57	0.314
Women	6/113 (5.3)	3/119 (2.5)	2.17	0.65-2.75	0.426	1.32	0.30-5.73	0.712
				LR X^2=0.15, p=0.701			Adjusted LR X^2=0.42, p=0.517	
Disrupted family arrangements								
Men	33/161 (20.5)	16/124 (12.9)	1.74	0.91-3.33	0.095	1.22	0.59-2.51	0.587
Women	23/110 (20.9)	15/91 (16.5)	1.34	0.65-2.75	0.426	1.16	0.52-2.56	0.716
				LR X^2= 0.26, p=0.610			Adjusted LR X^2=0.12, p=0.734	
Multiple adversities								
Men	50/172 (29.1)	19/137 (13.9)	**2.33**	1.69-3.21	**<0.001**	**1.92**	1.35-2.55	**<0.001**
Women	32/113 (28.3)	26/119 (21.8)	1.31	0.94-1.83	0.108	1.17	0.81-1.70	0.406
				LR X^2= **6.39**, p=**0.041**			Adjusted LR X^2=4.97, p=0.083	

*Adjusted for age at interview, ethnicity and level of education. CI, confidence interval. LR X^2, Likelihood ratio chi-squared test. OR, odds ratio.

There were two significant gender interactions, namely for severe physical abuse (p=0.033) and for multiple adversities (p=0.041). Male psychosis cases were more than twice as likely to report severe physical abuse as male controls (OR=2.33), whilst no association was present amongst female participants (OR=0.85). Male psychosis cases were also more than twice as likely to report two or more adversities as male controls (OR=2.33). A trend for interaction effect by gender was also found for parental separation (p=0.089), again with more than a two-fold greater prevalence amongst male psychosis cases compared to their controls (OR=3.06), and a weaker trend for the association in women (OR=1.64). Institutional care (OR=3.29) and disrupted family arrangements (OR=1.74) were all more commonly reported by male psychosis cases than their controls, though the association remained at a trend level. A trend in the association between parental loss and psychosis was detected both in male (OR=2.11) and female (OR=2.09) psychosis cases compared to their controls.

In the adjusted model, male psychosis patients were still more than two times more likely to report separation from mother or father than male controls (OR=2.19), but the interaction effect for gender fell short of statistical significance (p=0.288). Furthermore, the significant gender interactions for severe physical abuse (p=0.097) and multiple adversities (p=0.083) decreased to a trend level. Male psychosis cases were more than three times as likely to report experiences of sexual abuse as male controls (OR=3.14), whilst no association was present amongst female participants (OR=1.01). However, the strength of the association between sexual abuse and psychosis did not reach statistical significance for interaction by gender (p=0.069). No significant associations in men or women were found for institutional care or disrupted family arrangements, with no interactions by gender.

Association between childhood adversity and psychosis modified by ethnicity

The associations between types of childhood adversity and psychosis caseness were also analysed to determine if they differed according to ethnic group. Due to the small number of controls of Black African (n=32) and Black Caribbean (n=39) origins compared to White British control group (n=102), Black African and Black Caribbean groups were put together in these analyses. The prevalence of different adversities for psychosis cases and controls by ethnic groups, White British (n=174) and Black (n=192), along with the unadjusted and adjusted odds ratios for association with psychosis case status, is shown in Table 4.4. This table also contains the results of the likelihood ratio tests conducted to assess presence of an interaction with ethnicity.

Table 4.4 Prevalence of childhood adversity amongst psychosis cases and controls by ethnicity

Ethnicity	Patients *n* (%)	Controls *n* (%)	Unadjusted OR	95% CI	*p* value	Adjusted[a] OR	95% CI	*p* value
Parental separation								
White British	27/71 (38.0)	25/102 (24.5)	1.89	0.98-3.64	0.058	1.44	0.70-2.97	0.316
Black	86/120 (71.7)	34/70 (48.6)	**2.68**	1.45-4.95	**0.002**	**2.30**	1.17-4.54	**0.016**
				LR χ^2=0.58, p=0.448			Adjusted LR χ^2=0.93, p=0.335	
Parental loss								
White British	6/71 (8.4)	8/102 (7.8)	1.08	0.36-3.27	0.885	0.69	0.20-2.42	0.563
Black	15/119 (12.6)	4/70 (5.7)	2.38	0.76-7.48	0.138	1.84	0.54-6.27	0.327
				LR χ^2=0.97, p=0.324			Adjusted LR χ^2=1.35, p=0.246	
Physical abuse								
White British	14/72 (19.4)	13/102 (12.7)	1.65	0.72-3.77	0.232	1.54	0.61-3.93	0.363
Black	31/121 (25.6)	11/70 (15.7)	1.85	0.86-3.96	0.114	1.36	0.59-3.17	0.469
				LR χ^2=0.04, p=0.845			Adjusted LR χ^2=0.05, p=0.825	
Sexual abuse								
White British	11/72 (15.3)	8/102 (7.8)	2.12	0.81-5.57	0.128	3.10	0.97-9.90	0.056

Ethnicity	Patients *n* (%)	Controls *n* (%)	Unadjusted OR	95% CI	*p* value	Adjusted[a] OR	95% CI	*p* value
Black	17/121 (14.0)	9/70 (12.9)	1.11	0.46-2.64	0.817	1.08	0.42-2.78	0.866
				LR χ^2=0.95, p=0.329			Adjusted LR χ^2=1.95, p=0.163	
Institutional care								
White British	4/72 (5.6)	5/102 (4.9)	1.14	0.29-4.41	0.848	0.73	0.18-3.00	0.660
Black	4/121 (3.3)	0/71 (0.0)	N/A	---	---	---	---	---
				LR χ^2 N/A			LR χ^2 N/A	
Disrupted family arrangements								
White British	10/67 (14.9)	10/81 (12.3)	1.25	0.49-3.20	0.648	0.76	0.27-2.12	0.604
Black	30/116 (25.9)	12/64 (18.7)	1.51	0.71-3.21	0.282	1.34	0.59-3.04	0.482
				LR χ^2=0.10, p=0.753			LR χ^2=0.72, p=0.396	
Multiple adversities								
White British	16/72 (22.2)	16/102 (15.7)	1.45	0.98-2.15	0.061	1.22	0. 97-1.88	0.354
Black	40/121 (33.1)	13/71 (18.3)	**2.17**	1.40-3.35	**<0.001**	**1.73**	1.08-2.76	**0.021**
				LR χ^2=2.18, p=0.335			LR χ^2=2.09, p=0.351	

*Adjusted for gender, age at interview and level of education. – indicates unable to calculate values due to at least one cell containing a zero value. CI, confidence interval. LR χ^2, Likelihood ratio chi-squared test. OR, odds ratio.

Within the main ethnic groups, psychosis cases of Black African or Caribbean origins were more than two times as likely as their respective controls to report parental separation (OR=2.68) or more than two adversities during childhood (OR=2.17). A smaller non-significant trend effect was also evident for this form of adversity amongst White British participants (OR=1.89) but no significant interaction effect was found (p=0.147). Similarly, psychosis cases of Black African or Caribbean origins were also more than two times as likely as their respective controls to report a history of parental loss during childhood (OR=2.38), although the association (p=0.138) as well as the interaction effect (p=0.324) did not reach statistical significance. Additionally, reports of severe physical abuse were approximately two times more commonly reported by Black African or Caribbean cases than Black African or Caribbean controls (OR=1.85) but the association remained at a weak trend level (p=0.114). A trend effect was also evident for the association between childhood sexual abuse and psychosis amongst White British participants (OR=2.19), but no interaction by ethnicity was found (p=0.329).

After adjusting for demographic confounders, the association between parental separation (p=0.016), multiple adversities (p=0.021) and psychosis in Black African or Caribbean participants remained significant. Moreover, childhood sexual abuse was three times more prevalent in White British cases compared to controls following adjustment for confounders (OR=3.10), though this failed to reach conventional levels of significance (p=0.056) and no interaction with ethnicity was found (p=0.163).

Childhood adversity and psychosis diagnosis

Baseline diagnoses were available on 218 psychosis cases with a complete CECA.Q from the GAP study. Of these cases, 150 (68.8%) had an ICD-10 diagnosis of non-affective psychosis, 42 (19.3%) of affective psychosis, and the rest of the cases (n=26, 11.9%) were classified as 'other psychosis', but this latter diagnostic group was not included in the following analysis due to its heterogeneous nature. The odds ratios for the association between each type of adversity and psychosis are shown in Table 4.5 separately for cases with schizophrenia spectrum disorders and those with affective psychoses calculated in comparison to the non-psychotic control group.

Table 4.5 Prevalence of childhood adversity for each diagnostic category compared to controls

Type of childhood adversity by diagnosis	**Cases *n/N* (%)**	**Controls *n/N* (%)**	**Unadjusted OR**	**95% CI**	***P***	**Adjusted OR***	**95% CI**	***P***
Parental separation								
Non-affective psychosis	81/148 (54.7)	91/255 (35.7)	**2.18**	1.44-3.29	**<0.001**	**2.06**	1.32-3.23	**<0.001**
Affective psychosis	22/42 (52.4)	91/255 (35.7)	**1.98**	1.03-3.83	**0.041**	1.96	0.99-3.91	0.054
Parental loss								
Non-affective psychosis	23/148 (15.5)	16/255 (6.3)	**2.75**	1.40-5.39	**0.003**	**3.02**	1.44-6.35	**0.003**
Affective psychosis	0/41 (0.0)	16/255 (6.3)	N/A	---	---	---	---	---
Physical abuse								
Non-affective psychosis	37/150 (24.7)	39/254 (15.5)	**1.80**	1.09-2.99	**0.022**	1.54	0.89-2.65	0.122
Affective psychosis	4/42 (9.5)	39/254 (15.5)	0.58	0.20-1.72	0.326	0.61	0.20-1.85	0.382
Sexual abuse								
Non-affective psychosis	21/150 (14.0)	28/254 (11.0)	1.31	0.72-2.41	0.377	1.46	0.75-2.83	0.265
Affective psychosis	7/42 (16.7)	28/254 (11.0)	1.61	0.65-3.98	0.298	1.71	0.66-4.43	0.268

Type of childhood adversity by diagnosis	Cases *n/N* (%)	Controls *n/N* (%)	Unadjusted OR	95% CI	*P*	Adjusted OR*	95% CI	*P*
Institutional care								
Non-affective psychosis	8/150 (5.3)	5/256 (1.9)	2.83	0.91-8.81	0.073	2.47	0.75-8.19	0.137
Affective psychosis	2/42 (4.8)	5/256 (1.9)	2.51	0.47-13.38	0.281	2.44	0.44-13.46	0.306
Disrupted family arrangements								
Non-affective psychosis	28/141 (19.9)	31/215 (14.4)	1.47	0.84-2.58	0.179	1.48	0.81-2.70	0.197
Affective psychosis	8/40 (20.0)	31/215 (14.4)	1.48	0.63-3.52	0.370	1.37	0.55-3.39	0.497
Multiple adversities								
Non-affective psychosis	45/150 (30.0)	45/256 (17.6)	**3.42**	1.98-5.92	**<0.001**	**2.64**	1.43-4.84	**0.002**
Affective psychosis	10/42 (23.8)	45/256 (17.6)	1.60	0.69-3.73	0.272	1.47	0.59-3.67	0.404

*Adjusted for gender, age at interview, ethnicity and level of education. – indicates unable to calculate values due to at least one cell containing a zero value. CI, confidence interval. OR, odds ratio.

Reports of parental separation were significantly elevated in both diagnostic groups compared to controls. However, after adjusting for gender, age at interview, ethnicity and level of education, the association between parental separation and affective psychosis diagnosis just fell short of statistical significance (p=0.054). Parental loss was more prevalent in cases with a non-affective psychosis diagnosis than controls (OR=2.75), and the association remained significant after adjustment for confounders (p=0.003). No association could be calculated for cases with affective psychosis due to none of these cases having reported parental death. Similarly, reports of severe physical abuse (OR=1.85) and two or more adversities (OR=3.42) were more prevalent in cases with non-affective psychosis diagnosis than controls, while there was a non-significant trend for such a history to be less common in affective psychosis cases than controls (OR=0.58). There was a non-significant trend for institutional care to be reported more than twice as often by both case with non-affective (OR=2.83) and affective psychosis (OR=2.51) diagnoses. However, no associations were found between childhood sexual abuse or disrupted family arrangement and the presence of either diagnosis. The lack of statistically significant effects may have been due to the small numbers of patients in each category.

From Table 4.5, it is also apparent that between the two diagnostic categories, the prevalence of reports of parental separation, sexual abuse, institutional care and disrupted family arrangements were very similar for cases with non-affective psychosis and those with an affective diagnosis. However, non-affective psychosis cases reported higher rates of exposure to parental death (15.5% vs 0%, respectively) and physical abuse (24.7% vs. 9.5%, respectively) than affective psychosis cases. Calculation of an OR for parental death was not possible due to the zero number of affective cases with exposure, but for physical abuse a stronger association with non-affective psychosis diagnosis than affective psychosis diagnosis was confirmed by logistic regression analysis (OR= 3.11, 95% CI 1.04-9.30, p=0.042).

Childhood adversity and psychosis dimensions

Previous studies on the dimensionality of the Positive and Negative Syndrome Scale (PANSS) have frequently produced evidence on 5 dimensions of psychosis (Reininghaus et al., 2013; Emsley et al., 2003). Therefore, after extraction, I decided to retain the five factors for rotation as all had eigenvalues (variance that each standardised variable contributes to a factor extraction) greater than or close to 1.0. Factor loadings for the PANSS items with factor loading values > 0.4 are presented in Table 4.6, along with the percentage of the variance explained, eigenvalues and Cronbach's α reliability.

Table 4.6 Factor loadings for a multidimensional model of psychosis using PANSS items

PANSS Items	Negative symptoms	Disorganisation	Mania	Positive symptoms	Depression
Blunted affect	0.81				
Emotional withdrawal	0.79				
Poor rapport	0.75				
Passive social withdrawal	0.74				
Lack of spontaneity	0.70				
Motor retardation	0.48				
Active social avoidance	0.56				
Conceptual disorganization		0.64			
Stereotyped thinking		0.71			
Mannerisms and posturing		0.62			
Poor attention		0.47			
Disturbance of volition		0.43			
Preoccupation		0.42			
Excitement			0.47		
Hostility			0.60		
Uncooperativeness			0.72		
Delusions				0.78	
Hallucinatory behavior				0.55	
Suspiciousness				0.57	
Anxiety					0.70
Guilt feelings					0.54
Tension					0.53
Depression					0.65
Variance explained (%)	31.2	30.6	22.3	22.0	15.2
Eigenvalue	5.54	3.87	1.98	1.30	0.93
α	0.86	0.76	0.68	0.68	0.70

PANSS, Positive and Negative Syndrome Scale.

Descriptive names have been assigned to each factor obtained according to the items (symptoms) loading on each of them: the first factor reflected negative symptoms of psychosis and accounted for 31.2% of the variance (loading value range: 0.482 to 0.814); the second factor reflected disorganised symptoms and accounted for 30.6% of the variance (loading value range: 0.423 to 0.710); the third factor reflected manic symptomatology and accounted for 22.3% of the variance (loading value range: 0.475 to 0.723); the fourth factor reflected positive symptoms and accounted for 22% of the variance (loading value range: 0.553 to 0.777); the fifth factor included depressive symptomatology and accounted for 15.2 of the variance (loading value range: 0.533 to 0.703). Factors showed overall good consistency as indicated by the values of Cronbach α (bottom part Table 4.6).

Table 4.7 presents linear regression findings on the associations between each type of childhood adversity and the factor scores for these five psychosis dimensions.

Table 4.7 Association between psychosis dimensions and types of childhood adversity

Type of adversity	Negative symptoms			Disorganisation			Mania			Positive symptoms			Depression		
	β	B	95% CI	β	B	95% CI	β	B	95% CI	β	B	95% CI	β	B	95% CI
Parental separation	0.06	0.11	-0.18-0.39	0.06	0.10	-0.13-0.32	0.05	0.07	-0.15-0.29	0.11	0.30	-0.09-0.69	-0.04	-0.07	-0.35-0.21
Parental loss	0.05	0.14	-0.27-0.57	0.00	0.00	-0.33-0.33	-0.06	-0.11	-0.44-0.21	-0.05	-0.20	-0.77-0.37	0.04	0.10	-0.31-0.51
Physical abuse	0.05	-0.12	-0.46-0.27	0.01	0.03	-0.25-0.31	0.00	0.01	-0.26-0.27	0.12	0.38	-0.09-0.86	0.05	0.11	-0.22-0.46
Sexual abuse	0.07	-0.18	-0.57-0.21	**0.18**	**0.40***	0.08-0.71	0.10	0.20	-0.10-0.51	**0.18**	**0.67***	0.14-1.20	0.05	0.14	-0.25-0.53
Institutional care	0.11	0.45	-0.16-1.06	-0.03	-0.09	-0.58-0.41	0.01	-0.04	-0.52-0.44	-0.01	-0.08	-0.94-0.77	-0.08	-0.35	-0.96-0.26
Family arrangements	0.06	-0.14	-0.50-0.21	-0.08	-0.16	-0.45-0.14	0.01	0.02	-0.26-0.31	-0.11	-0.39	-0.88-0.13	-0.00	-0.01	-0.37-0.35

*p<0.05. β, standardised beta coefficient, B, regression coefficient, CI, confidence interval.

It can be seen from Table 4.7 that there were no significant associations between reported histories of parental separation, physical abuse or disrupted family arrangements before 17 years of age and scores for the negative, mania and depression symptom dimensions in this sample. However, patients reporting childhood sexual abuse were more likely to score higher on the positive (p=0.013) and disorganised (p=0.013) symptom dimensions compared to those patients that did not report such abuse exposure. Furthermore, results showed an indication of a trend in the association between severe sexual abuse and manic symptoms (p=0.183). An indication of a trend was also found in the association between parental separation (p=0.132), physical abuse (p=0.133), disrupted family arrangements (p=0.146) and scores on the positive symptom dimension as well as in the association between being taken into local authority care and scores on the negative symptom dimension (p=0.147).

Childhood adversity and specific psychosis symptoms

Next, associations between childhood sexual abuse and specific psychotic symptoms from the positive and disorganised symptom dimensions that cut across diagnostic categories were explored. Analyses were limited to this type of adversity as it was the only adverse childhood experience to demonstrate a statistically significant association with these symptom dimensions in the previous model (Table 4.7). Around half of patients reporting severe sexual abuse experienced hallucinations (15/28, 53.6%), delusions (14/28, 50.0%) and suspiciousness or persecution (14/28, 50.0%), and these positive symptoms were also the most prevalent. For ease of analysis, each symptom group from the PANSS was converted into a binary variable, with scores from 1 to 3 coded as 0 (indicating absent, minimal or mild symptoms) and scores from 4 to 7 being recoded as 1 (indicating moderate, moderate severe, severe or extreme symptoms). The odds ratios for associations between this adversity variable and specific psychotic symptoms are shown in Table 4.8.

Table 4.8 Prevalence of childhood sexual abuse for individual psychotic symptoms in the disorganised and positive symptom dimensions

Type of psychotic symptom	Present *n/N* (%)	Absent *n/N* (%)	Unadjusted OR	95% CI	*P*	Adjusted OR*	95% CI	*P*
Disorganised symptom dimension								
Conceptual disorganization	7/32 (21.9)	21/150 (14.0)	1.72	0.66-4.48	0.267	1.72	0.64-4.61	0.278
Stereotyped thinking	7/23 (30.4)	21/160 (13.1)	**2.90**	1.07-7.87	**0.037**	**3.14**	1.11-8.87	**0.031**
Mannerisms and posturing	1/5 (20.0)	27/178 (15.2)	1.39	0.15-12.99	0.768	1.32	0.12-13.62	0.818
Poor attention	5/17 (29.4)	23/166 (13.9)	2.59	0.83-8.04	0.099	2.58	0.77-8.67	0.125
Disturbance of volition	3/8 (37.5)	24/173 (13.9)	3.72	0.83-16.61	0.085	4.39	0.94-20.58	0.061
Preoccupation	5/36 (13.9)	23/146 (15.7)	0.86	0.30-2.45	0.781	0.91	0.31-2.71	0.872
Positive symptom dimension								
Delusions	14/83 (16.87)	14/100 (14.0)	1.25	0.56-2.79	0.592	1.31	0.56-3.04	0.527
Hallucinatory behaviour	15/65 (23.08)	13/116 (11.2)	**2.38**	1.05-5.37	**0.038**	2.30	1.00-5.28	0.050
Suspiciousness	14/63 (22.22)	14/119 (11.76)	2.14	0.95-4.84	0.067	2.35	0.96-5.18	0.061

*Adjusted for gender, age at interview, ethnicity and level of education. CI, confidence interval. OR, odds ratio.

Significant associations were found between experiences of sexual abuse and stereotyped thinking, with a three-fold increased prevalence of this specific type of disorganised symptom (OR=3.14). Furthermore, there was a significant association between reports of childhood sexual abuse and hallucinatory behaviour (p=0.038), with more than two-fold increased prevalence of this type of positive symptom (OR= 2.38).

Indeed, there were evidence of trends for poor attention levels (p=0.099) and suspiciousness (p=0.067) to be approximately twice as common amongst patients reporting childhood sexual abuse compared to those who did not report such adversity. Reports of sexual abuse demonstrated a trend (p=0.085) for over three-fold increased odds of disturbance of volition (OR=3.72). No significant associations were found between reports of sexual abuse and conceptual disorganization (p=0.267), mannerisms and posturing (p=0.768), preoccupation (p=0.781) and delusions (0.592). These findings remained largely the same following adjustment for demographic confounders. Specifically, the association between childhood sexual abuse and stereotyped thinking remained significant (p=0.031) and increased in magnitude (OR=3.14), while the size of the association with hallucinatory behaviour was similar after adjustment but was borderline significant (p=0.050). Furthermore, there was still evidence of a trend in the association between childhood sexual abuse and disturbance of volition (p=0.061), suspiciousness (p=0.061) and poor attention (p=0.125).

Childhood adversity and psychotic-like experiences (PLEs)

As explained in the Methodology Chapter 3, endorsement of one or more symptoms (hypomania, thought insertion, paranoia, strange experiences, hallucinations) using the criteria outlined by Morgan et al. (2009) was considered to indicate the presence of psychotic-like experiences (PLEs). PLEs data from the PSQ was available for 203 of the 256 controls that had completed the CECA.Q in the GAP study. These controls were slightly more male (n=111, 54.7%), White British (n=74, 36.5%), had some form of qualification (n=197, 97.0%) and a mean

age of 27.8 years (sd=8.6; range 18-64 years). The controls with and without full PSQ data did not differ in terms of gender (X^2=0.534, p=0.465) but there was a significant difference in ethnicity (X^2=21.81, p=0.026) and age (t=4.85, p<0.001). The final model was, therefore, adjusted for ethnicity and age at interview along with the other demographic confounders. The proportion of controls endorsing PLEs by each form of childhood adversity along with the association between childhood adversity and PLEs is presented in Table 4.9.

Table 4.9 Associations between different types of childhood adversity and psychotic-like experiences (PLEs) in controls

Type of childhood adversity	**PLEs present** *n/N* **(%)**	**PLEs absent** *n/N* **(%)**	**Unadjusted OR**	**95% CI**	***p* value**	**Adjusted*** **OR**	**95% CI**	***p* value**
Parental separation	16/24 (66.7)	57/178 (32.0)	**4.25**	1.72-10.50	**0.002**	**3.88**	1.51-9.97	**0.005**
Parental loss	0/0 (0)	13/178 (7.30)	N/A	---	---	---	---	---
Physical abuse	8/24 (33.3)	25/178 (14.0)	**3.06**	1.19-7.90	**0.021**	**3.07**	1.16-8.15	**0.024**
Sexual abuse	5/24 (20.8)	15/178 (8.43)	2.86	0.93-8.75	0.066	**3.81**	1.13-12.83	**0.031**
Institutional care	2/24 (8.3)	3/179 (1.7)	5.33	0.84-33.69	0.075	5.40	0.75-38.77	0.093
Disrupted family arrangements	6/19 (31.6)	17/146 (11.6)	**3.50**	1.16-10.43	**0.024**	2.89	0.93-9.04	0.067
Total adversity								
1	7/24 (29.2)	61/179 (34.1)	1.80	0.58-5.60	0.312	1.67	0.52-5.38	0.390
2 or more	11/24 (45.8)	24/179 (13.4)	**7.18**	2.41-21.38	**<0.001**	**7.36**	2.35-23.11	**<0.001**

*Adjusted for gender, age at interview, ethnicity and level of education. CI, confidence interval; OR, odds ratio; PLEs, psychotic-like experiences.

Approximately 1 in 10 of the control sample endorsed at least one PLE on the PSQ (n=24, 11.8%). Around 20% of controls who reported separation from parents during childhood also reported experiencing at least one PLE in the past year which was over four times greater than the prevalence of PLEs amongst who did not report parental separation (OR=4.25), and the association held after adjustment for demographic confounders (p=0.005). A robust association with PLEs was also found for childhood physical abuse, with PLEs being experienced about three times as often by those with compared to those without a history of this form of adversity. There was a trend for over a two-fold increased rate of PLEs amongst controls who reported childhood sexual abuse (OR=2.86), which increased (OR=3.81) and reached the statistical significance in the adjusted model (0.031). Reports of disrupted family arrangements were associated with over a three-fold increase in experiencing at least one PLE (OR=3.50), however the association only reached a trend level after adjustment for confounders (0.067). Although both unadjusted and adjusted odds ratios were elevated for institutional care, they only reached trend level of significance. There were no controls who reported death of parent who also reported experiencing at least one PLE; therefore it was not possible to examine such association.

The association with PLEs was much stronger for participants who reported multiple (OR=7.18, 95% CI 12.41-21.38, p<0.001) than single (OR=1.80, 95% CI 0.58-5.60, p=0.312) adverse childhood experiences, and the association remained significant also adjusting for demographic confounders. A score test for trend provided, in fact, evidence for a linear trend (z=3.67, p<0.001) indicating a dose-response effect for multiple adverse experiences. Unfortunately, the numbers were too low to look at associations between types of childhood adversity and specific PLEs separately.

Discussion

Childhood adversity and psychosis onset

Over three-quarters of the psychosis cases (71.2%) in this sample reported at least one form of adversity occurring before 17 years of age compared to around half of the healthy control participants (50.8%). These results confirmed the broad association between reports of childhood adversity and clinical psychotic disorders that has been reported by numerous previous studies (see Varese et al., 2012a for a meta-analysis of these studies). The most prevalent form of adversity amongst cases and controls was separation for at least six months from either parent (56.5% vs. 35.7%, respectively). In terms of childhood abuse, physical abuse from either parent was more common than sexual abuse (cases: 22.8% vs. 14.4%; controls: 15.3% vs. 11.0%, respectively). Very few participants in this sample reported being taken into care during childhood (cases: 4.9%; controls: 2.0%) or experiencing the death of a parent (cases: 11.7%; controls: 6.3%). Several of these adverse experiences, namely parental separation, parental loss and physical abuse, were found to be significantly associated with psychosis case status, and these associations held following adjustment for demographic confounders (with the exception of physical abuse). Furthermore, experiences of institutional care demonstrated a non-significant trend for more than a two-fold association with psychosis caseness even after adjustment for demographic confounders. Experiences of sexual abuse and disrupted family arrangements were more prevalent amongst psychosis patients compared to controls, though the magnitude of these associations remained weak.

These results are in line with previous studies conducted on the association between specific types of childhood adversity and psychosis. In fact, separation from either or both parents has been associated with increased risk of illness onset (Agid et al., 1999; Bebbington et al., 2004; Friedman et al., 2002; Morgan et al., 2007; Mortensen et al., 1999; Parnas et al., 1985; Rubino et al., 2009; Wicks et al., 2005). Recently, Morgan et al. (2014b) showed a robust association between separation and loss of parent with psychosis caseness in the

AESOP sample, as was the case in our clinical sample, with a similar two-fold elevation in risk. In line with previous research showing that childhood physical abuse predicted presence of psychosis (e.g., Fisher et al., 2010; Shevlin et al., 2007a) a significant association has been found with childhood physical abuse before adjustment for confounders. In contrast with previous studies that highlighted a significant association between sexual abuse and risk of psychosis (Bebbington et al., 2004, 2011; Cutajar et al., 2010; Janssen et al., 2004), this was not found to be the case in our clinical sample.

The dose-response effect of childhood adversity on psychosis onset found in this sample is in contrast with results from AESOP study conducted on a similar first-episode psychosis sample (Fisher et al., 2009; 2010), which found no evidence for dose-response effects for multiple versus single trauma-exposures. However, Shevlin et al. (2007a; 2008), found that experiencing 2 or more types of childhood adversities (including childhood neglect, sexual and physical abuse) significantly increased the likelihood of psychosis on two large community samples.

Reports of physical abuse and experiences of multiple adversities were higher amongst male than female psychosis cases, though following adjustment for the other demographic confounders no significant interaction with gender remained. Similarly, parental separation was more prevalent amongst male than female psychosis cases, and this significant association held following adjustment for the other demographic confounders; but no interaction with gender was found. Reports of sexual abuse were more prevalent amongst female than male participants and this was particularly pronounced amongst the psychosis cases. Interestingly, following adjustment for the other demographic confounders, a significant association between sexual abuse and caseness was found amongst men but not women; but the interaction effect remained at a trend level of significance. These results are consistent with those reported in a general population survey conducted in the UK, which found that males experienced more victimisation by peers, more physical violence from non-caregivers, and

more exposure to community violence, while females reported more experiences of sexual victimisation than males (Radford et al., 2013). Moreover, the stronger association found between sexual abuse and psychosis amongst male patients is in line with Shevlin et al.'s (2007a) study, which found that the associations between rape and psychosis were significantly higher for male participants (OR=5.81, 95% CI=1.24–27.17; z=4.99, p=0.02) than female participants (OR=4.05, 95% CI=2.02– 8.08; z=5.67, p<0.001) with a significant interaction by gender

However, higher rates of childhood abuse in inpatient samples than those reported here has been found in previous studies. For instance, Morgan and Fisher (2007) reported average rates of childhood sexual abuse for female and male patients with a psychotic disorder were 42% and 28% respectively, and rates of childhood physical abuse of 35% and 38% respectively. By contrast, in the current study female and male reported rates for sexual abuse were 18.6% and 11.6% respectively, and 14.2% and 28.5% for physical abuse respectively. However, one reason for the discrepancy is that the Morgan and Fisher (2007) review included patients with more chronic forms of psychosis. Indeed the rate found in the current study are much more similar to those reported for a first-episode psychosis sample from a partially overlapping geographical area: 27% of women and 8% of men had reported sexual abuse and 27% of women and 20% of men had reported physical abuse (Fisher et al., 2009).

Despite a significantly higher prevalence of parental separation and multiple adversities amongst Black (African and Caribbean) than White British participants, no significant interactions with ethnicity were found for the associations with psychotic disorder. This replicates the separation results on the AESOP sample reported by Morgan et al. (2007) and a previous study conducted on a similar geographical sample that found greater prevalence of maternal separation amongst African-Caribbeans, than White British psychosis cases (Mallett et al., 2002). In terms of abuse, sexual abuse was more prevalent amongst White British psychosis patients, though no significant interactions with

ethnicity were found. Therefore, the differential prevalence of separation and multiple adversities between ethnic groups could possibly provide a partial explanation for the higher rates of psychosis that have previously been found amongst the Black group in this part of the UK (Fearon et al., 2006) and amongst the Black population more broadly in the UK (Cooper, 2005; Sharpley et al., 2001). However, the findings from this study can only be considered as speculative due to the small number of participants in each ethnic group and the inability to include other ethnic groups (such as Asian groups) due to insufficient sample size.

Childhood adversity, psychosis diagnosis and symptoms

In summary, no specificity was found overall between type of childhood adversity and psychosis diagnosis. Reported parental separation was associated with both non-affective psychosis and affective psychosis diagnoses, though the association with the latter fell short of statistical significance, after adjusting for demographic confounders, probably due to the small number of cases in this diagnostic group. The findings are also consistent with other studies where parental separation showed links with schizophrenia and other psychosis diagnoses (Agid et al., 1999; Barr et al. cited in Olin & Mednick, 1996; Kessler et al., 1997, Wicks et al., 2005). Morgan et al. (2007) have previously shown in a larger sample of the first-episode psychosis patients that separation from a parent was associated with both affective and non-affective psychosis diagnoses. In the current study experiences of parental loss were found to be robustly associated with non-affective psychosis diagnoses but it was not possible to investigate the association with affective psychosis because of the small sample size.

Some degree of specificity was found between reported physical abuse and psychotic diagnosis, with a significant association between this type of childhood adversity and non-affective psychosis. Cases with non-affective psychosis were more than three times more likely to report experiences of

physical abuse compared to cases with an affective psychosis diagnosis. This is in line with previous studies that have found childhood physical abuse to be more prevalent amongst individuals with schizophrenia (Compton et al., 2004; Gearon et al., 2003; Lysaker et al., 2004; Rosenberg et al., 2007; Schenkel et al., 2005) compared to patients with affective psychosis (Hammersley et al., 2003; Hlastala & McClellan, 2005; Neria et al., 2005), although Matheson et al. (2013) found no difference in their meta-analysis. The lack of a significant association found between childhood sexual abuse and affective psychosis is contrary to previous studies that have demonstrated a strong link between this type of adversity and depression (Bifulco et al., 1991) or bipolar disorders (Maniglio et al., 2013) compared to healthy individuals.

However, some specificities were found at the symptom clusters level. Reports of sexual abuse were found to be associated significantly with the cognitive disorganization and positive symptom dimensions. Moreover, exploring further the association between childhood sexual abuse and individual symptoms, a specific association between this type of adversity and stereotyped thinking as well as with hallucinatory behaviour was found. These findings are in line with previous studies that have suggested that childhood sexual abuse may be a particularly potent risk factor for hallucinations, a finding that has been reported both in the general population (Bentall et al., 2012; Shevlin et al., 2007b; Sitko et al., 2014) as well as clinical samples (Hammerseley et al., 2003; Read & Argyle, 1999; Read et al., 2003; Sommer et al., 2012).

Furthermore, thought disorder seems to be associated with a history of childhood maltreatment or neglect (Toth et al., 2011). In the current study associations were found at a trend level with disturbance of volition and suspiciousness; this could of course be a chance finding. Other studies have, however, pointed to chronic victimisation and discrimination as possible specific causes of paranoid symptoms (Janssen et al., 2003; Mirovsky & Ross, 1983) as result of damaged early attachment relationships (Bowlby, 1965; 1973).

Childhood adversity and psychotic-like experiences (PLEs)

Prevalence rates of childhood adversity in the control sample (12%) were similar to those reported in studies of the UK general population (Radford et al. 2011). The prevalence of PLEs in the current sample (11.8%) was slightly lower than that reported in another sample from an overlapping geographical areas (Morgan et al., 2009). The prevalence of PLEs was higher amongst controls that reported childhood adversity in the current sample than amongst those without such a history. More specifically, childhood parental separation and physical abuse were significantly associated with PLEs. These findings are in line with previous research that showed a higher prevalence of PLEs with both separation from parents (Morgan et al., 2009; Scott et al., 2009) and experiences of physical abuse (Gracie et al., 2007; Kelleher et al., 2008; Nishida et al., 2008; Ross & Joshi, 1992; Shevlin et al., 2007c; Thompson et al., 2009; Whitfield et al., 2005). After adjustment for demographic confounders the association between sexual abuse and PLEs also became significant, which is consistent with existing findings (Gracie et al., 2007; Kelleher et al., 2008; Lataster et al., 2006; Ross & Joshi, 1992; Shevlin et al., 2007c; Spauwen et al., 2006; Startup, 1999; Thompson et al., 2009; Whitfield et al., 2005). Furthermore, a trend was detected for being in institutional care and disrupted family arrangements during childhood and PLEs.

Interestingly, a dose-response relationship between childhood adversity and psychotic-like experiences was found, with the odds of psychotic-like experiences increasing in line with increasing levels of childhood adversities. This result confirms previous findings, where a cumulative effect was observed between number of childhood adversities and risk for non-clinical psychotic experiences (Arseneault et al., 2011; Heins et al., 2011; Janssen et al., 2004; Kelleher et al., 2013; Lataster et al., 2006; Schreier et al., 2009).

Overall, these results are mainly consistent with the findings for psychotic disorder presented previously and support the hypothesis of an aetiological continuity between subclinical psychotic experiences and psychotic disorder (Johns & van Os, 2001; Shevlin et al., 2007b; van Os et al., 2009), such that the same risk factors associated with the expression of clinical psychosis are also

found to more commonly occur amongst individuals in non-clinical populations who have PLEs.

Results section 4.2

Childhood adversity and one-year outcomes

Association between childhood adversity and course of psychosis

The 285 patients enrolled in the GAP study with completed childhood adversity assessments, have been followed up for one year starting from the first contact with psychiatric services for psychosis using the Electronic Patient Journey System (EPJS). Figure 4.1 shows the attrition rate of this follow-up.

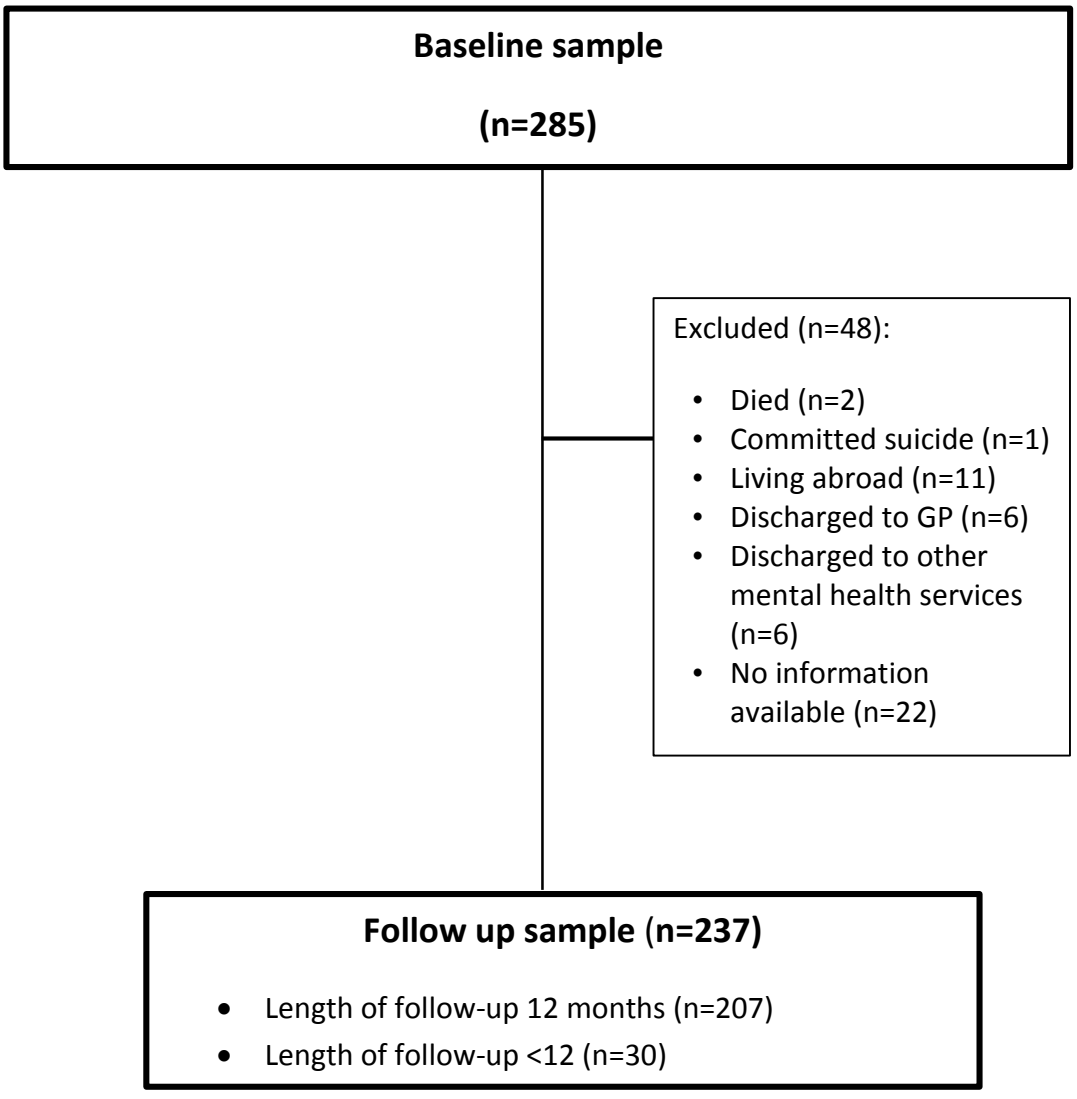

Figure 4.1 Flow chart of one-year follow-up attrition rate

A total of 237 psychosis cases were successfully followed-up up to 12 months, giving a completion rate of 83.2%. Patients were followed up a mean of 11.3 months (SD=2.23) after first contact with mental health services for psychosis. It was possible to retrieve information throughout the 12 month period from first contact with mental health services for 207 cases (73% of baseline sample). Follow-up information were not available for 16.8% of baseline sample (n=48) and the reasons for drop out included: leaving the country (n=11), discharged to a General Practitioner (n=6) or other mental health services (n=6), no information available on EPJS (n= 22) and death (n=3, including one patient who completed suicide).

When patients with follow-up information available were compared with those without, there was no evidence of systematic differences by demographic characteristics including gender (χ^2=2.584, p=0.145), age at interview (t=-0.247, p=0.805), ethnicity (χ^2=10.673, p=0.470) and educational attainment (χ^2=5.584, p=0.235). Furthermore, there were no differences between patients followed up over one year and those without follow-up information in terms of baseline relationship status (χ^2=0.349, p=0.693), employment status (χ^2=0.004, p=1.000), and GAF-disability score (t=-0.828, p=0.409). Similarly, patients with follow-up data did not significantly differ in terms of clinical functioning at baseline (duration of untreated psychosis in weeks t=1.146, p=0.253; GAF-symptom score t=-0.724; 0.470) or diagnosis (χ^2=1.104, p=0.622). Additionally, the follow-up sample did not significantly differ from the baseline sample in terms of their reported prevalence of parental separation (χ^2=1.005, p=0.341), parental loss (χ^2=0.540, p=0.621), physical abuse (χ^2=2.217, p=0.186), sexual abuse (χ^2=1.717, p=0.260), institutional care (χ^2=0.069, p=1.000) or disrupted family arrangements (χ^2=0.197, p=0.693). Therefore, there appear to be no systematic biases in the follow-up sample in terms of demographic or clinical characteristics nor in terms of childhood adversity history.

Childhood adversity and clinical outcomes

The Follow-up Psychiatric and Personal History Schedule (FU-PPHS, Sartorius et al., 1986) defines remission as a state following a psychotic episode, in which none of the symptoms listed as characteristics of a psychotic episode are present for a period of 30 days or more (a definition of psychotic episode according to FU-PPHS criteria has been provided in Chapter 3). During a remission a patient may exhibit a variety of non-psychotic symptoms (e.g. depressed mood, neurotic manifestations) or some of the so called negative symptoms, or be entirely symptoms free (incomplete or complete remission). The rating of remission (as well as a rating of a psychotic episode) was based only on ascertainable absence (or presence) of psychotic symptoms and not on whether the patient was taking any psychotropic medication or not, or whether he was hospitalized or not.

Over the first year of contact with mental health services a total of 123 (55.1%) patients had no relapse episodes and remitted from psychotic symptoms, 50 (22.0%) had one or more relapses, and a total of 52 (22.9%) were characterised by continuous psychotic illness. Table 4.10 presents the results of ordered logistic regressions exploring the associations between each type of childhood adversity and course of psychosis during this one-year period.

Table 4.10 Association between childhood adversity and course of illness throughout the one year follow-up period

Type of childhood adversity	No relapses, complete or nearly complete recovery n (%)	One or more relapses n (%)	Continuous illness n (%)	OR	95% CI	*P*	Adjusted OR*	95% CI	*P*
Parental separation									
No (n=97)	56 (57.7)	21 (21.6)	20 (20.6)	1.0	-	-	-	-	-
Yes (n=128)	68 (53.1)	29 (22.7)	31 (24.2)	1.21	0.73-2.02	0.459	1.25	0.56-2.78	0.583
Parental loss									
No (n=200)	108 (54.0)	48 (24.0)	44 (22.0)	1.0	-	-	-	-	-
Yes (n=24)	15 (62.5)	2 (8.3)	7 (29.2)	0.87	0.36-2.07	0.755	0.39	0.10-1.58	0.187
Physical abuse									
No (n=176)	101 (57.4)	38 (21.6)	37 (21.0)	1.0	-	-	-	-	-
Yes (n=51)	24 (47.7)	12 (23.5)	15 (29.4)	1.53	0.85-2.76	0.156	1.02	0.36-2.86	0.973
Sexual abuse									
No (n=193)	105 (54.4)	43 (22.3)	45 (23.3)	1.0	-	-	-	-	-
Yes (n=34)	20 (58.8)	7 (20.6)	7 (20.6)	0.84	0.41-1.71	0.632	1.06	0.33-3.39	0.918
Institutional care									
No (n=216)	116 (53.7)	49 (22.7)	51 (23.6)	1.0	-	-	-	-	-

Type of childhood adversity	No relapses, complete or nearly complete recovery n (%)	One or more relapses n (%)	Continuous illness n (%)	OR	95% CI	*P*	Adjusted OR*	95% CI	*P*
Yes (n=11)	9 (81.8)	1 (9.1)	1 (9.1)	0.26	0.05-1.24	0.092	0.43	0.04-4.43	0.473
Family arrangements									
Up to 2 (n=173)	98 (56.7)	35 (20.2)	40 (23.1)	1.0	-	-	-	-	-
3 or more (n=46)	23 (50.0)	12 (26.1)	11 (23.9)	1.22	0.66-2.24	0.531	0.74	0.27-2.02	0.558
Total adversity									
0 (n=65)	39 (60.0)	16 (24.6)	10 (15.4)	1.0	-	-	-	-	-
1 (n=92)	46 (50.0)	20 (21.7)	26 (28.3)	1.64	0.89-3.04	0.112	1.09	0.45-2.65	0.847
2 or more (n=70)	40 (57.1)	14 (20.0)	16 (22.9)	1.23	0.63-2.37	0.544	0.77	0.27-2.20	0.632

*Adjusted for duration of untreated psychosis (DUP) and T0 Global Assessment of Functioning Scale (GAF-Symptoms). OR, Odds Ratio, CI, confidence interval.

Childhood history of parental separation, parental loss, physical abuse, sexual abuse, and disrupted family arrangements were not associated with course of psychosis over the one-year follow-up period. No evidence for a dose-response effect of childhood adversity on illness course was found.

A total of 155 patients (67.1%) had a period of at least 30 days without psychotic symptoms during the first year of contact with mental health services. Table 4.11 presents results of the association between each type of childhood adversity and remission from psychotic symptoms.

Table 4.11 Association between childhood adversity and remission from psychotic symptoms for at least 30 days over the one year of illness

Type of childhood adversity	Remission n (%)	No remission n (%)	OR	95% CI	*P*	Adjusted OR*	95% CI	*P*
Parental separation								
No (n=98)	66 (67.3)	32 (32.6)	1.0	-	-	-	-	-
Yes (n=131)	88 (67.2)	33 (32.8)	0.99	0.57-1.73	0.978	0.99	0.42-2.33	0.982
Parental loss								
No (n=202)	136 (67.3)	66 (32.7)	1.0	-	-	-	-	-
Yes (n=26)	17 (65.4)	9 (34.6)	0.92	0.39-2.16	0.843	1.84	0.49-6.77	0.361
Physical abuse								
No (n=176)	119 (67.6)	57 (32.4)	1.0	-	-	-	-	-
Yes (n=55)	36 (65.4)	19 (34.5)	0.91	0.48-1.72	0.766	1.00	0.35-2.90	0.998
Sexual abuse								
No (n=196)	131 (66.8)	65 (33.2)	1.0	-	-	-	-	-
Yes (n=35)	24 (68.6)	11 (31.4)	1.08	0.50-2.34	0.841	0.87	0.26-2.92	0.819
Institutional care								
No (n=220)	146 (66.4)	74 (33.6)	1.0	-	-	-	-	-
Yes (n=11)	9 (81.8)	2 (18.2)	2.28	0.48-10.83	0.299	2.50	0.25-25.06	0.437

Type of childhood adversity	Remission n (%)	No remission n (%)	OR	95% CI	*P*	Adjusted OR*	95% CI	*P*
Family arrangements								
Up to 2 (n=174)	116 (66.7)	58 (33.3)	1.0	-	-	-	-	-
3 or more (n=48)	31 (64.6)	17 (35.4)	0.91	0.47-1.78	0.787	1.92	0.62-5.94	0.256
Total adversity								
0 (n=65)	44 (67.7)	21 (32.3)	1.0	-	-	-	-	-
1 (n=93)	61 (65.6)	32 (34.4)	0.91	0.46-1.78	0.783	1.53	0.60-4.04	0.390
2 or more (n=73)	50 (68.5)	23 (32.5)	1.04	0.51-2.12	0.920	1.51	0.50-4.57	0.468

*Adjusted for duration of untreated psychosis (DUP) and T0 Global Assessment of Functioning Scale (GAF-Symptoms). CI, confidence interval. OR, odds ratio.

It is apparent from Table 4.11 that reported exposure to parental separation, parental loss, physical abuse, sexual abuse and disrupted family arrangements was not associated with symptomatic remission. However, patients with history of institutional care were more than two times more likely to report remission from psychotic symptoms, though the association did not reach statistical significance (p=0.299). The adjusted model did not show any change in the regression analyses in terms of statistical significance. However, controlling for DUP and baseline symptom severity resulted in increases in the odds of remission amongst patients who reported a history of parental loss or disrupted family arrangements, though neither associations reached statistical significance. No difference in terms of remission was found for participants who reported multiple than single adverse childhood experiences, indicating no dose-response effect for repeated adverse experiences.

In terms of symptoms severity, a total of 138 (55%) patients reported moderate or severe psychotic symptoms one year after the first episode of illness (defined as GAF scores below 61). The mean GAF symptoms score for the overall sample was 58.5 with a standard deviation of 19.7. The results of linear regressions of the associations between each type of childhood adversity and GAF symptom score at one-year follow-up are shown in Table 4.12.

Table 4.12 Association between childhood adversity and overall clinical functioning at one-year follow-up

Type of childhood adversity	GAF symptoms Mean (SD)	B	95% CI	*P*	Adjusted B*	95% CI	*P*
Parental separation							
No (n=93)	59.3 (18.63)	1.0	-	-	-	-	-
Yes (n=119)	58.0 (20.63)	-1.37	-6.77-4.03	0.617	-7.14	-15.49-1.20	0.092
Parental loss							
No (n=187)	58.0 (19.17)	1.0	-	-	-	-	-
Yes (n=24)	60.2 (24.22)	2.22	-6.24-10.68	0.606	**18.72**	6.60-30.84	**0.003**
Physical abuse							
No (n=164)	58.7 (19.36)	1.0	-	-	-	-	-
Yes (n=50)	57.7 (28.94)	-1.04	-7.32-5.25	0.745	-1.98	-12.47-8.51	0.708
Sexual abuse							
No (n=181)	58.4 (19.84)	1.0	-	-	-	-	-
Yes (n=33)	58.8 (19.19)	0.31	-7.05-7.67	0.934	-0.81	-12.84-11.21	0.893
Institutional care							
No (n=204)	58.1 (19.68)	1.0	-	-	-	-	-
Yes (n=10)	67.0 (18.89)	8.9	-3.62-21.47	0.162	10.83	-9.28-30.95	0.288

Type of childhood adversity	GAF symptoms Mean (SD)	B	95% CI	*P*	Adjusted B*	95% CI	*P*
Family arrangements							
Up to 2 (n=162)	59.0 (19.71)	1.0	-	-	-	-	-
3 or more (n=43)	55.8 (20.52)	-3.13	-9.86-3.59	0.360	1.30	-9.68-12.29	0.814
Total adversity							
0 (n=62)	59.6 (17.72)	1.0	-	-	-	-	-
1 (n=85)	57.5 (19.80)	-2.10	-8.61-4.41	0.526	-2.31	-12.02-7.38	0.636
2 or more (n=67)	58.8 (21.40)	-0.80	-7.67-6.06	0.818	2.71	-8.49-13.91	0.632

*Adjusted for duration of untreated psychosis (DUP) and T0 Global Assessment of Functioning Scale (GAF-Symptoms). B, regression coefficient; CI, confidence interval; GAF, Global Assessment of Functioning scale.

From Table 4.12, it can be seen that there were no associations with GAF-symptom scores for parental separation, parental loss, physical abuse, sexual abuse or disrupted family arrangements. However, there was a non-significant trend for patients who reported experiencing institutional care to have less severe symptoms (as indicated by a higher GAF score) at one year from contact with services (p=0.162). After adjustment for DUP and baseline GAF symptom scores, experiences of parental loss significantly predicted lower symptom levels at one year (p<0.001). A linear trend was also found in the adjusted model between experiences of parental separation and more severe psychotic symptoms at one year (p=0.092). Also for psychotic symptoms at one year follow-up there was no evidence of a dose-response effect for repeated adverse experiences.

A mixed group factorial ANOVA was performed in a subsample of first-episode psychosis patients (n=110) with available data on both GAF-symptom at time of interview (T_0) and at follow-up (T_1) to examine whether the change in GAF-symptoms scores differed within cases reporting experiences of childhood adversity and those cases that did not report such experiences. There was no significant difference in terms of course of symptoms between cases reporting parental separation, $F(1,107)=0.616$, p=0.434, physical abuse, $F(1, 109)=0.740$, p=0.392, or multiple adversities, $F(2, 108)=0.786$, p=0.458, compared to cases who did not report such experiences. Furthermore, GAF-symptom scores did not significantly differ between T_0 and T_1 in cases with disrupted family arrangements compared to those who had not such adversity, $F(1, 106)=0.336$, p=0.563. Similarly, no effect of institutional care on T_0-T_1 GAF symptoms and was found, $F(1, 109)=0.862$, p=0.355.

A trend between parental loss and course of symptoms over 12 months was found, $F(1, 108)=2.075$, p=0.153, as well as a trend effect for sexual abuse was also found, $F(1, 109)=2.232$, p=0.138.

Childhood adversity and social outcomes

A total of 165 (70.8%) patients were not involved in a steady relationship over the first year after first psychosis onset. Table 4.13 shows results of the association between each type of childhood adversity and relationship status at one year.

Table 4.13 Association between childhood adversity and relationship status at follow-up

Type of childhood adversity	In a relationship n (%)	Not in a relationship n (%)	Unadjusted OR	95% CI	*P*	Adjusted OR*	95% CI	*P*
Parental separation								
No (n=100)	33 (33.0)	67 (67.0)	1.0	-	-	-	-	-
Yes (n=131)	34 (25.9)	97 (74.1)	1.40	0.79-2.49	0.243	1.16	0.56-2.39	0.655
Parental loss								
No (n=207)	61 (29.5)	146 (70.5)	1.0	-	-	-	-	-
Yes (n=23)	7 (30.4)	16 (69.6)	0.95	0.37- 2.44	0.923	0.84	0.27-2.63	0.765
Physical abuse								
No (n=179)	56 (31.3)	123 (68.7)	1.0	-	-	-	-	-
Yes (n=54)	12 (22.2)	42 (77.8)	1.59	0.78-3.26	0.202	**2.82**	1.07-7.43	**0.035**
Sexual abuse								
No (n=199)	61 (30.7)	138 (69.3)	1.0	-	-	-	-	-
Yes (n=34)	7 (20.6)	27 (79.4)	1.70	0.78-3.26	0.237	1.33	0.48-3.74	0.583
Institutional care								
No (n=222)	66 (29.7)	156 (70.3)	1.0	-	-	-	-	-
Yes (n=11)	2 (18.2)	9 (81.8)	1.90	0.40-9.05	0.418	1.79	0.30-10.44	0.521

Type of childhood adversity	In a relationship n (%)	Not in a relationship n (%)	Unadjusted OR	95% CI	*P*	Adjusted OR*	95% CI	*P*
Family arrangements								
Up to 2 (n=179)	52 (29.1)	127 (70.9)	1.0	-	-	-	-	-
3 or more (n=45)	15 (33.3)	30 (66.7)	0.81	0.41-1.65	0.575	0.85	0.34-2.07	0.716
Total adversity								
0 (n=67)	22 (32.8)	45 (67.2)	1.0	-	-	-	-	-
1 (n=96)	30 (31.2)	66 (68.8)	1.07	0.55-2.10	0.831	0.93	0.40-2.13	0.861
2 or more (n=70)	16 (22.9)	54 (77.1)	1.65	0.77-3.51	0.194	1.56	0.61-3.99	0.348

*Adjusted for T0 relationship status. CI, confidence interval. OR, odds ratio.

Patients reporting history of parental separation, physical, sexual abuse or institutional care were more likely to be not in a steady relationship one year after illness onset than those without a history of such adversities, though the associations did not reach statistical significance (all *p*'s>0.200). After adjustment for relationship status at baseline, experiences of physical abuse were significantly associated with not being in a relationship at follow up (*p*=0.035), with almost a three-fold increase in odds compared to patients who did not report such childhood experience (OR=2.82).

Participants not in a steady relationship at follow-up were more likely to report multiple (OR=1.65, 95% CI 0.77-3.51, *p*=0.194) than single (OR=1.07, 95% CI 0.55-2.10, *p*=0.831) adverse childhood experiences, though the association did not reach statistical significance, also after adjustment for relationship status at baseline, and no evidence for a linear trend (z=1.29, *p*=0.197) was found. Analyses were also conducted in the subgroup of patients with completed follow-up data at 12 months only (n=207). Results of the association between childhood adversity and relationship status at 12 months were largely unchanged in this subgroup (See Appendix XVII).

A total of 169 (75.1%) patients of the overall sample were unemployed at one year. Table 4.14 shows the prevalence rates of employment by type of childhood adversity, along with their associations.

Table 4.14 Association between childhood adversity and employment status at follow-up

Type of childhood adversity	**Employed n (%)**	**Not employed n (%)**	**Unadjusted OR**	**95% CI**	***P***	**Adjusted OR***	**95% CI**	***P***
Parental separation								
No (n=96)	27 (28.1)	69 (71.9)	1.0	-	-	-	-	-
Yes (n=127)	28 (22.0)	99 (78.0)	1.38	0.75-2.55	0.298	0.97	0.48-1.96	0.932
Parental loss								
No (n=201)	47 (23.4)	154 (76.6)	1.0	-	-	-	-	-
Yes (n=21)	8 (38.1)	13 (61.9)	0.50	0.19-1.27	0.143	0.52	1.17-1.53	0.234
Physical abuse								
No (n=177)	47 (26.6)	130 (73.4)	1.0	-	-	-	-	-
Yes (n=48)	9 (18.7)	39 (81.3)	1.57	0.75-3.48	0.270	1.67	0.67-4.17	0.273
Sexual abuse								
No (n=191)	48 (25.1)	143 (74.9)	1.0	-	-	-	-	-
Yes (n=34)	8 (23.5)	26 (76.5)	1.09	0.46-2.57	0.842	0.96	0.37-2.49	0.928
Institutional care								
No (n=214)	52 (24.3)	162 (75.7)	1.0	-	-	-	-	-
Yes (n=11)	4 (36.4)	7 (63.6)	0.56	0.16-1.99	0.373	0.47	0.11-1.99	0.304

Type of childhood adversity	Employed n (%)	Not employed n (%)	Unadjusted OR	95% CI	*P*	Adjusted OR*	95% CI	*P*
Family arrangements								
Up to 2 (n=174)	48 (27.6)	126 (72.4)	1.0	-	-	-	-	-
3 or more (n=42)	8 (19.0)	34 (81.0)	1.62	0.70-3.75	0.260	1.54	0.60-3.92	0.365
Total adversity								
0 (n=66)	20 (30.3)	46 (69.7)	1.0	-	-	-	-	-
1 (n=93)	21 (22.6)	72 (77.4)	1.49	0.73-3.05	0.274	0.84	0.36-1.95	0.687
2 or more (n=66)	15 (22.7)	51 (77.3)	1.48	0.67-3.22	0.325	1.14	0.47-2.75	0.774

*Adjusted for T0 employment status. CI, confidence interval. OR, odds ratio.

There were no significant associations with unemployment status at one-year follow-up for cases reporting a history of childhood adversity compared to those who did not. These results were unchanged in the adjusted model, after controlling for baseline employment, and no evidence of a dose-response effect for repeated adverse experiences was found. Analyses were also conducted in the subgroup of patients with completed follow-up data at 12 months (n=207). Results of the association between childhood adversity and employment status at 12 months were largely unchanged in this subgroup (See Appendix XVIII).

In terms of overall social functioning at one year, a total of 169 (67.3%) patients reported moderate or severe disability one year after the first episode of illness (defined as GAF-disability scores below 61). The mean GAF disability score was 55 with a standard deviation of 19.5. The results of linear regressions examining associations between each form of childhood adversity and GAF disability scores are presented in Table 4.15.

Table 4.15 Associations between childhood adversity and social/vocational functioning at one-year follow-up

Type of childhood adversity	GAF disability Mean (SD)	B	95% CI	*P*	Adjusted B*	95% CI	*P*
Parental separation							
No (n=93)	54.7 (19.49)	1.0	-	-	-	-	-
Yes (n=119)	55.3 (19.71)	0.65	-4.70-6.00	0.811	-1.12	-9.48-7.25	0.791
Parental loss							
No (n=187)	54.4 (18.82)	1.0	-	-	-	-	-
Yes (n=24)	59.6 (24.15)	5.17	-3.16-13.50	0.222	**22.64**	11.03-34.28	**<0.001**
Physical abuse							
No (n=164)	55.3 (19.56)	1.0	-	-	-	-	-
Yes (n=50)	54.4 (19.50)	-0.95	-7.18-5.27	0.764	-0.46	-11.04-10.12	0.931
Sexual abuse							
No (n=181)	55.3 (19.38)	1.0	-	-	-	-	-
Yes (n=33)	54.1 (20.46)	-1.11	-8.40-6.19	0.765	-3.41	-15.10-8.27	0.563
Institutional care							
No (n=204)	54.5 (19.41)	1.0	-	-	-	-	-
Yes (n=10)	67.3 (18.35)	**12.81**	0.45-25.17	**0.042**	12.42	-7.33-32.17	0.215

Type of childhood adversity	GAF disability Mean (SD)	B	95% CI	*P*	Adjusted B*	95% CI	*P*
Family arrangements							
Up to 2 (n=162)	54.93 (19.48)	1.0	-	-	-	-	-
3 or more (n=43)	56.42 (20.47)	1.49	-5.17-8.15	0.659	3.63	-7.21-14.46	0.508
Total adversity							
0 (n=62)	55.4 (19.7)	1.0	-	-	-	-	-
1 (n=85)	53.5 (18.0)	-1.98	-8.42-4.45	0.545	0.41	-9.42-10.23	0.935
2 or more (n=67)	56.8 (21.3)	1.35	-5.44-8.14	0.695	6.67	-4.33-17.68	0.231

*Adjusted for duration of untreated psychosis (DUP) and T0 Global Assessment of Functioning Scale (GAF-Disability). B, regression coefficient; CI, confidence interval; GAF, Global Assessment of Functioning scale.

There were no significant associations with GAF-disability scores for those patients reporting experiences of parental separation, parental loss, physical abuse, sexual abuse or disrupted family arrangements in childhood compared to those patients who did not report such experiences. Being in institutional care was significantly associated with better functioning (as indicated by higher GAF disability scores) at one year after presentation to mental health services (B=12.81), though this association became non-significant following adjustment for confounders (p=0.215). After adjustment for DUP and baseline GAF disability scores, experiences of parental loss significantly predicted better functioning at one year (p<0.001), though the confidence intervals were very wide (11.03-34.28) indicating that this result should be interpreted cautiously. No evidence of a cumulative effect for repeated adverse experiences on GAF-disability score was fund.

A mixed group factorial ANOVA was performed in a subsample of first-episode psychosis patients (n=110) with available data on both GAF-disability at time of interview (T_0) and at follow-up (T_1) to examine whether the change in GAF-disability scores differed within cases exposed to each type of childhood adversity and those cases that did not report such experiences. There was no significant effect of parental separation, F(1, 106)=0.026, p=0.871, physical abuse, *F*(1, 109)=1.122, p=0.292, and sexual abuse, *F*(1, 108)=0.041, p=0.840, on course of social and vocational functioning throughout the year of follow-up. GAF-symptom scores did not significantly differ between T_0 and T_1 in cases with disrupted family arrangements, F(1, 105)=0.118, p=0.732, or those reporting multiple adversities, F(2, 107)=1.460, p=0.237, compared to those who had not such adversities. A trend in the effect of institutional care on GAF disability scores was found, *F*(1, 108)=2.514, p=0.116.

As reported in the linear regressions analyses, a significant effect of parental loss on social course was found, *F*(1, 107)=7.341, p=0.008. This indicates

that GAF-symptom scores increased over follow-up time in patients reporting parental loss compared to those who did not.

Childhood adversity and service use

A total of 18 cases (7.6% of the 236 on whom information was available) were never admitted to a psychiatric ward at any point during the follow-up period including initial episode of illness. The median length of admission for the majority of patients who were admitted was 48.5 days spent in hospital, with a mean of 69.7 days with a standard deviation of 68.9. As discussed in Chapter 3, due to the skewed nature of the admission days, the number of days that patients spent on a psychiatric ward was dichotomised at the median into less than 49 days versus 49 days or more. Results of the association between childhood adversity and length of hospital admission are showed in Table 4.16.

Table 4.16 Associations between childhood adversity and length of hospital admission over one year follow-up

Type of childhood adversity	Less than 49 days n (%)	49 days or more n (%)	OR	95% CI	*P*	Adjusted OR*	95% CI	*P*
Parental separation								
No (n=98)	59 (60.2)	39 (39.8)	1.0	-	-	-	-	-
Yes (n=136)	59 (43.4)	77 (56.6)	**1.97**	1.16-3.35	**0.012**	**2.45**	1.06-5.66	**0.035**
Parental loss								
No (n=207)	103 (49.7)	104 (50.2)	1.0	-	-	-	-	-
Yes (n=26)	13 (50.0)	13 (50.0)	0.99	0.44-2.24	0.981	0.67	0.19-2.35	0.536
Physical abuse								
No (n=178)	91 (51.1)	87 (48.8)	1.0	-	-	-	-	-
Yes (n=58)	27 (46.5)	31 (53.4)	1.20	0.66-2.17	0.546	1.42	0.51-4.00	0.504
Sexual abuse								
No (n=199)	99 (49.7)	100 (50.2)	1.0	-	-	-	-	-
Yes (n=37)	19 (51.3)	18 (48.6)	0.94	0.46-1.89	0.858	0.74	0.22-2.46	0.619
Institutional care								
No (n=224)	110 (49.1)	114 (50.9)	1.0	-	-	-	-	-
Yes (n=12)	8 (66.7)	4 (33.3)	0.48	0.14-1.65	0.245	0.64	0.10-4.16	0.637

Type of childhood adversity	Less than 49 days n (%)	49 days or more n (%)	OR	95% CI	*P*	Adjusted OR*	95% CI	*P*
Family arrangements								
Up to 2 (n=178)	89 (50.0)	89 (50.0)	1.0	-	-	-	-	-
3 or more (n=48)	21 (43.7)	27 (56.2)	1.29	0.68-2.44	0.443	1.60	0.55-4.71	0.390
Total adversity								
0 (n=66)	40 (60.6)	26 (39.4)	1.0	-	-	-	-	-
1 (n=95)	47 (49.5)	48 50.5)	1.57	0.83-2.97	0.164	2.36	0.89-6.20	0.081
2 or more (n=75)	31 (41.3)	44 (58.7)	**2.18**	1.11-4.29	**0.023**	2.28	0.77-6.79	0.139

*Adjusted for duration of untreated psychosis (DUP) and T0 Global Assessment of Functioning Scale (GAF-Symptoms). OR, odds ratio. CI, confidence interval.

There was a significant association between experiences of parental separation in childhood and a longer admission to a psychiatric ward during one-year follow-up, with cases reporting such adversity being approximately twice as likely to have longer hospital stays compared to those without such a history (p=0.012). No significant associations with admission length were found for those cases reporting history of parental loss, physical and sexual abuse, institutional care or disrupted family arrangements. Results did not change after adjustment for DUP and baseline GAF symptoms. The association with length of hospital admission over one year follow-up was stronger for participants who reported multiple (OR=2.18, 95% CI 1.11-4.29, p=0.023) than single (OR=1.57, 95% CI 0.83-2.97, p=0.164) adverse childhood experiences. A score test for trend provided, in fact, evidence for a linear trend (z=2.27, p=0.023) indicating a dose-response effect for repeated adverse experiences. However, the association attenuated at a trend level of statistical significance after adjustment for clinical confounders.

A total of 9 (4.4%) patients followed-up were not in treatment with psychiatric medications one-year after first contact with mental health services for psychosis. The majority (n=104, 50.5%) of psychosis patients were treated with novel antipsychotics or with a combination of a novel antipsychotic and an antidepressant (n=40, 19.4%).

Amongst those patients in treatment with medications, a total of 132 patients (64%) were compliant, defined as the extent to which the patient followed the advice given to him with regard to prescribed treatment, in terms of regularity of intake and dosage. Non-compliance was defined as drugs irregular intake (with lapses for at least 3 days occurring more than once) or in an inadequate dosage (too low), or when prescribed drugs were not taken at all. Table 4.17 presents odds ratios for the association between each type of childhood adversity and compliance with medication at follow-up.

Table 4.17 Associations between childhood adversity and compliance with medications at one year follow-up

Type of childhood adversity	Compliant n (%)	Not compliant n (%)	OR	95% CI	*P*	Adjusted OR*	95% CI	*P*
Parental separation								
No (n=86)	61 (70.9)	25 (29.1)	1.0	-	-	-	-	-
Yes (n=118)	69 (58.5)	49 (41.5)	1.73	0.96-3.13	0.069	**2.34**	1.11-4.92	**0.026**
Parental loss								
No (n=181)	117 (64.6)	64 (35.4)	1.0	-	-	-	-	-
Yes (n=22)	12 (54.5)	10 (45.5)	1.52	0.63-3.72	0.355	1.18	0.39-3.57	0.766
Physical abuse								
No (n=159)	102 (64.5)	57 (35.8)	1.0	-	-	-	-	-
Yes (n=47)	30 (63.8)	17 (36.2)	1.01	0.51-2.00	0.968	1.23	0.50-3.01	0.659
Sexual abuse								
No (n=179)	118 (65.9)	61 (34.1)	1.0	-	-	-	-	-
Yes (n=27)	14 (51.9)	13 (48.1)	1.80	0.79-4.06	0.159	1.50	0.51-4.35	0.458
Institutional care								
No (n=196)	106 (66.7)	53 (33.3)	1.0	-	-	-	-	-
Yes (n=10)	21 (51.2)	20 (48.8)	0.75	0.19-3.01	0.690	1.25	1.20-7.83	0.813

Type of childhood adversity	**Compliant n (%)**	**Not compliant n (%)**	**OR**	**95% CI**	***P***	**Adjusted OR***	**95% CI**	***P***
Family arrangements								
Up to 2 (n=159)	106 (66.7)	53 (33.3)	1.0	-	-	-	-	-
3 or more (n=41)	21 (51.2)	20 (48.8)	1.90	0.95-3.81	0.069	2.67	1.00-7.17	0.051
Total adversity								
0 (n=58)	43 (74.1)	15 (25.9)	1.0	-	-	-	-	-
1 (n=87)	51 (58.6)	36 (41.4)	2.02	0.98-4.18	0.057	**2.81**	1.15-6.84	**0.023**
2 or more (n=61)	38 (62.3)	23 (37.7)	1.73	0.79-3.80	0.168	2.22	0.82-6.05	0.117

*Adjusted for duration of untreated psychosis (DUP) and compliance with medication at baseline. CI, confidence interval. OR, odds ratio.

Evidence of almost a two-fold increased odds of non-compliance with medications was found amongst those patients who reported childhood exposure to parental separation (OR=1.73), sexual abuse (OR=1.80) or disrupted family arrangements (OR=1.73). There was no evidence of an association with compliance with medication for those patients who reported experiences of parental loss, physical abuse, or being in an institutional care compared to those who had not. Following adjustment for DUP and compliance with medication at baseline, parental separation became significantly associated with medication non-compliance at one year follow-up (p=0.026). In the adjusted model, the association with medication adherence at one year was significant for participants who reported single (OR=2.81, 95% CI 1.15-6.84, *p*=0.023) but not multiple (OR=2.22, 95% CI 0.82-6.05, *p*=0.117) adverse childhood experiences, indicating no dose-response effect for repeated adverse experiences.

Discussion

Childhood adversity and clinical course of psychosis

In summary, 45% of the overall sample had episodes of relapse from psychotic symptoms over one year from first contact with mental health services. Similar rates of relapse within one year after first-episode psychosis have been reported in previous follow-up studies (Kam et al., 2013; Novak-Grubic & Tavcar, 2002; Uçok et al., 2006).

There was a higher prevalence of continuous illness in those cases reporting experiences of parental separation, parental loss and physical abuse, compared to those who did not report such experiences. However, there were no significant associations with illness course for these two subgroups of psychosis patients. These results do not confirm previous findings based on chronic (Garno et al., 2005; Lecomte et al., 2008; Alvarez et al*.,* 2011) as well as first-episode psychosis (Alvarez-Jimenez et al., 2011; 2012) patients that

reported an association between exposure to childhood adversity and a more chronic course of illness.

Similarly, 67% of psychosis cases experienced a period of remission from psychotic symptoms of at least 30 days over the first year of illness. Experiences of childhood adversity were not predictive in terms of remission from symptoms, with no significant associations between types of adversity and symptomatic remission. This is in contrast with studies conducted in different clinical populations. A meta-analysis of epidemiological studies conducted in patients with depression showed that maltreated individuals were twice as likely as those without a history of childhood maltreatment to develop both recurrent and persistent depressive episodes (OR=1.78; Nanni et al. 2012). A similar pattern has been shown in samples of bipolar disorder patients: those reporting history of childhood abuse reported higher severity level of current manic symptoms, and faster cycling frequencies over a period of up to two years (Garno et al., 2005; Leverich et al., 2002; Neria et al., 2005). However, focusing on studies conducted on first episode psychosis patients, childhood abuse does not seem to be associated with symptomatic remission at follow-up (Conus et al., 2010) and this was also the case in the current study.

In terms of overall clinical functioning measured with the GAF-symptoms scale, there were no significant differences at baseline between cases reporting childhood adversity and level of impairment on clinical functioning compared to those that did not report any type childhood adversity (Mean: 44.93 vs 51.42 respectively, t=1.805, p=0.730). At follow-up, after adjusting for baseline GAF-symptom scores, parental loss predicted significantly better clinical functioning at one year follow-up, and a trend in the association between being in institutional care and lower symptom levels was also found. These findings are not consistent with previous studies. For example, Lysaker et al. (2005) compared, over the course of 4 months, symptom levels of psychosis patients with history of sexual abuse to those without such history. The abuse group had consistently higher levels of positive and emotional discomfort symptoms over

the follow-up period. Spauwen et al. (2006), in a two year follow-up study showed that experience of any trauma over the course of an individual's life was associated with the likelihood of suffering from 3 or more psychotic symptoms. Another prospective study of the Turkish population (Uçok & Bikmaz, 2007) reported an association between a general measure of childhood adversity (including physical, psychological, and sexual abuse, and psychological negligence) and more severe psychotic symptoms at six months follow-up. Unfortunately, it was not possible in the current study to test the association with severity of specific psychotic symptoms and this makes comparison with previous studies difficult.

Childhood adversity and social course of psychosis

Using employment and relationship status as indicators of functional outcomes, there was strong evidence that the marked social exclusion present among cases with reported childhood adversity at baseline (e.g., 51.5% of cases reporting history of childhood adversity were unemployed and 68.1% were not in a steady relationship) persisted through the follow-up period. These findings are partially in line with previous follow-up studies. For instance, results from the AESOP follow-up study (Morgan et al., 2014a) on a general sample of 532 incident first-episode psychosis patients found slightly higher rates in those who reported adversity in their follow-up over a period of ten years (68% of cases were single and 77.6% unemployed at follow-up).

Focusing on intra-group differences, a slightly higher proportion of cases reporting childhood adversity compared to those who did not report any adversity were not in a steady relationship at follow-up (72.3% vs 67.2%), though the difference did not reach statistical significance for any specific type of childhood adversity. After adjusting for relationship status at baseline, patients reporting experiences of physical abuse in childhood were almost three times

more likely not to be in a steady relationship at follow-up compared to those patients that did not report such adversity.

The rate of unemployment at follow-up was higher in those patients reporting at least one type of adversity compared to those that did not report such experiences (77.4% vs 69.7%, respectively). However, there was no significant effect of types of childhood adversity on the employment rate. This result does not confirm previous research that highlighted the link between childhood adversity and a higher rate of unemployment in patients with severe mental disorders at 18 months and two years respectively (Davidson et al., 2009; Alvarez et al., 2011). Lysaker et al. (2004) also reported that exposure to sexual abuse was associated with vocational deficits and poorer work performance over four weeks. Nonetheless, consistent with the current study, Conus et al. (2010) found that a history of sexual and/or physical abuse (SPA) amongst first-episode psychosis patients was not associated with functional remission, defined as employment based on paid or unpaid full- or part-time employment, being an active student in school or university, head of household with employed partner, or full or part-time volunteer.

In terms of global assessment of social and vocational functioning, there was a significant difference at baseline between cases reporting childhood adversities and higher impairment on social and vocational functioning compared to those that did not report childhood adversity (Mean: 53.70 vs 60.33 respectively, $t=2.157$, $p=0.033$). At follow-up, cases who reported being in institutional care during childhood had a significantly better social and vocational functioning compared to those who did not report such adversity. Moreover, following adjustment for baseline GAF-disability scores, parental loss predicted significantly better social and vocational functioning at one year follow-up, though the association with institutional care decreased to a trend level. These results are consistent with previous findings that have shown that first-episode psychosis patients exposed to sexual or physical abuse during childhood report lower premorbid social functioning but show no differences in terms of

functional outcome than non-exposed patients at 18 months follow-up (Conus et al., 2010).

However, Lysaker et al. (2001) reported that those with a diagnosis of schizophrenia and who reported a history of childhood sexual abuse had poorer psychosocial functioning in adulthood, had poorer role functioning and fewer of the psychological resources necessary for sustaining intimacy, and had high levels of emotional instability and turmoil. Davidson et al. (2009) found a relationship between trauma history and social functioning over time, the Trauma group's social functioning scores deteriorated over the 18 months, whereas the No Trauma group's scores improved. Furthermore, Stain et al. (2014) showed, in a sample of 223 first-episode psychosis patients, that childhood trauma was also associated with poorer premorbid functioning, and that exposure to interpersonal trauma was correlated with poorer social functioning in adulthood measured at illness onset.

However, these studies examining the association between childhood trauma and deficits in functioning were conducted in samples of chronic patients (Cusack et al., 2004; Davidson et al., 2009; Lysaker et al., 2001, 2004; Schenkel et al., 2005) or limited by their cross-sectional design (Stain et al., 2014).

Childhood adversity and service use

The median number of hospital admission days was 49 over the first year of illness with a higher prevalence of longer hospital stays in patients reporting experiences of childhood adversity compared to those who did not (53.4% vs 40.0% respectively). Specifically, a history of parental separation was significantly associated with longer hospital stays compared to those who did not report such childhood experiences, and a trend was also detected for disrupted family arrangements. This result is in line with a previous first-episode psychosis study, which found significant association between childhood abuse and longer stays in hospital (Greenfield et al., 1994). Another study on a broader sample of patients with severe mental illness found that childhood psychological abuse and

witnesses of domestic violence increased the risk of number of admittance at hospital (Alvarez et al., 2011). However, Davidson et al. (2009) found no significant differences between the 'Trauma' and 'No trauma' groups in terms of hospital admissions in a similar heterogeneous sample of psychiatric patients.

Parental separation significantly predicted also non-compliance with medications at one year from first contact with psychiatric services. In line with this result, a trend was also found for the association between disrupted caregiver arrangements and poor compliance with medications at follow-up. This is in line with a previous study, although conducted on a sample of a different type of patients (with HIV), showing that the death in childhood of an immediate family member significantly predicted non-adherence to antiretroviral therapies (Whetten et al., 2013). Having witnessed violence as a child was found to predict poor medication adherence in a sample of patients with early psychosis (Lecomte et al., 2008).

Methodological limitations

Although several studies have shown some bias in retrospective reports (Cohen et al., 1984), such bias is considered not sufficiently great to invalidate retrospective case-control studies of childhood experiences (Hardt et al., 2004). Moreover, previous studies have demonstrated that the effect of childhood adversity on psychosis remains significant regardless of study design (Varese et al., 2012a) and histories of childhood adversity obtained by psychosis patients appear reliable over time and unaffected by current symptoms (Fisher et al., 2011; Goodman et al., 1999; Read et al., 2005). Moreover, the assessment tool utilised in the current study is designed to minimise biased reporting. Every childhood experience section of the *Childhood Experiences of Care Abuse Questionnaire* (CECA.Q; Bifulco et al., 2005) begins with screening questions and then positive responses are followed up with more detailed questions. The CECA.Q elicits concrete examples of adverse experiences, and a guide has been published to score the severity of the responses in a standardised manner

(Bifulco et al., 2005). These factors ensure that the validity of the self-reported experiences is enhanced. Furthermore, this measure has been shown to have satisfactory levels of test–retest reliability and concurrent validity (Bifulco et al., 2005) even in those with psychosis (Fisher et al., 2011). This does not completely rule out biases in reporting but should have at least minimised it. Given the low prevalence rate of psychotic disorders in the general population (approximately 3%; van Os et al., 2009), it would not be feasible to attempt to collect data on childhood adversity prospectively in a birth cohort as the numbers required to obtain a sufficient number of cases would be too large to be cost-effective.

Only specific types of adversity occurring during childhood were investigated in this study. Other forms of childhood adversity, such as bullying and exposure to domestic violence (Fisher et al., 2013; Trotta et al., 2013), have also been previously associated with psychosis but it was not possible to investigate these within the current study due to a lack of detailed information on the timing and frequency or severity of exposure to these forms of adversity. Victimisation in childhood has been shown to be a strong predictor of exposure to victimisation and other stressful life events in adulthood (Korkeila et al., 2010) and these adult adverse experiences have been demonstrated to be associated with the onset of psychotic disorder (Beards et al., 2013; Bebbington et al., 1993, 1996; Morgan et al., 2014b). Therefore, it is plausible that adult adversity could at least partially account for the relationship found in this study between childhood adversity and psychosis. Unfortunately, although some information was collected about events occurring across the life-span in the current study, there was insufficient information to accurately date the age at which these events occurred and the number of participants with useable data was too small to permit analysis. Therefore, future studies should assess, explore and control for the presence of other adverse events in order to more robustly test the strength of the association between childhood adversity and psychosis in this sample.

From these cross-sectional data I cannot determine the direction of the relationship between childhood adversity and psychosis. However, I purposely only included childhood adversities that were reported as occurring before the age of 17 years in order to minimise the likelihood that they occurred after the psychosis onset. Indeed, our sample includes first episodes cases and healthy controls aged 18 or above. This does not entirely rule out the possibility of reverse causality and certainly it is possible that sub-clinical psychotic experiences or prodromal symptoms may have occurred during adolescence which may have preceded exposure to adversity. Thus the findings presented here should be considered with a reasonable amount of caution.

It was also not possible in this sample to explore whether depressed mood attenuated the main association between childhood sexual abuse and psychosis caseness (which has been previously investigated by Bebbington et al., 2004 and Shevlin et al., 2007a) as the level of depressive symptomatology was not assessed in the GAP sample. Moreover, negative perceptions of the self as well as anxiety, have also been found to partially mediate associations between early trauma and psychotic symptoms (Fisher et al., 2012; 2013), but again were unfortunately not assessed in this sample. Therefore, several psychological and biological mechanisms by which childhood trauma increases risk for psychosis that merit attention have not been investigated in this thesis. I have explored the potential role of genetic factors, however, and these findings are presented in subsequent chapters.

An important limitation of this study is represented by selection and information bias arising from loss to follow-up and missing or inaccurate data. In an attempt to minimize attrition, I was exhaustive in my effort to trace cases and to establish deaths and emigrations. I was able to determine the whereabouts or status of over 90% of the cohort. When I compared those with some information available on course and outcome for one year with those without, there was no strong evidence of systematic bias. Despite this does not entirely rule out selection bias, it does suggest attrition is unlikely to have seriously affected these

findings. Perhaps more problematic is the potential for information bias. The outcome data were obtained from clinical records rather than face-to-face interviews, thus limiting the type of outcomes that could be assessed. However, clinical ratings were made by consensus after careful consideration of all available information. I was careful to make ratings of presence or absence of symptoms only on the basis of clear and definite information. Patients do not always disclose symptoms to clinicians and clinicians do not always accurately record what patients say. Consequently, it is possible that clinical outcomes, such that periods of remission, course of illness and overall symptomatic functioning, collected from electronic records were under or overestimated. Finally, duration of follow-up was relatively short, and it is possible that impact of trauma on outcome may become manifest only later.

Conclusions

Despite these limitations, these findings provide important data for advancing our understanding of the aetiological factors underlying the onset and course of first episode psychosis. The project includes a sample of patients that had recently presented to mental health services with a psychotic disorder thus extending previous reports that used samples of chronic patients or examined psychotic symptoms or probable psychosis in the general population. Secondly, I have used a control group to compare the rates of childhood adversities against unlike many of the previous studies which only involved a sample of psychiatric patients. Additionally, I was able to examine associations between childhood adversities and psychosis independent of a range of potential confounders reported by previous literature including gender, age of onset, ethnicity and level of education attainment. Moreover, it could be argued that 12 month follow-up will be best accounted for by pre-existing prognostic factors. Accordingly, the association between childhood adversities and clinical and social outcomes over 12 months has been corrected for the influence of a wide range of known baseline prognostic indicators such as socio-demographic characteristics

(relationship and employment status at baseline), duration of untreated psychosis, and clinical and psycho-social assessment at baseline (obtained with Global Assessment of Functioning Scale; Endicott et al., 1976).

Synthesis of chapter 4

In summary, the analyses conducted in this chapter indicated that specific forms of childhood adversity were reasonably independently associated with both clinically-relevant psychotic disorder and non-clinical psychosis-like experiences in the samples studied. Following adjustment for all confounders, reported separation from father or mother for at least six months and death of a parent were two times more prevalent amongst psychosis patients when compared to geographically-matched controls. There was evidence that childhood traumatic experiences tended to co-segregate so that being exposed to one type of adversity increased the risk of exposure to another both in psychosis cases and controls reporting psychosis-like experiences. A significant gender interaction for severe physical abuse was found, with male psychosis cases being more than twice as likely to report this form of adversity as male controls. No interaction was found with ethnicity for the adversity-psychosis associations.

The specificity of the associations between adverse childhood experiences and clinical psychotic disorder in terms of diagnostic category and symptom dimensions were mixed. A stronger association between childhood physical abuse with non-affective than affective psychosis diagnosis was found. Patients reporting childhood sexual abuse were more likely to score higher on the positive and disorganised symptom dimensions compared to those patients that did not report such abuse exposure, with a significant association specifically with stereotyped thinking and hallucinatory symptoms.

Childhood adversity was not associated with clinical course of psychosis over the year from first contact with mental health services. In terms of social outcomes, experiences of physical abuse were significantly associated with almost a three-fold increase in odds of not being in a relationship at follow-up compared to patients who did not report such childhood experience. A significant association between experiences of parental separation in childhood and longer admissions to psychiatric wards during one-year follow-up and also a

two-fold increased odds of non-compliance with medication was found amongst those patients who reported childhood exposure to this adversity.

In Chapter 5, I will explore the impact of familial liability to mental illness on the associations between these adverse childhood experiences and psychosis and one-year outcomes.

CHAPTER 5 - Familial risk and childhood adversity interplay in the onset and course of psychosis

Aims of this chapter

The aim of this study was to extend existing research by investigating, for the first time, the interplay between various forms of childhood adversity and family psychiatric history in the onset and course of psychotic disorders. The specific aims are as follows:

1. To determine whether people with psychosis are more likely to have a parental history of psychosis and childhood adversity than unaffected controls.

2. To explore the possible synergistic effect of childhood adversity and familial liability in the onset of psychosis and its one-year course.

Results section 5.1

Family history, childhood adversity and psychosis onset

Sample characteristics

Information on family history of mental illness was available on 224 of the 285 psychosis cases and 250 of the 256 controls with a completed CECA-Q. The cases with and without FIGS data did not differ in terms of gender (χ^2=0.003, p=1.000), age (t=0.587, *p*=0.558), or diagnosis (χ^2=0.184, *p*=1.000). The basic demographic data by case and control status for those included in the analyses are presented in Table 5.1.

Table 5.1 Basic demographic characteristics of psychosis cases and controls.

Demographic variable	Cases (*N*=224) *n* (%)	Controls (*N*=250) *n* (%)	χ^2	df	p value
Gender			2.14	1	0.143
Men	135 (60.3)	134 (53.6)			
Women	89 (39.7)	116 (46.4)			
Ethnicity			**36.07**	**5**	**<0.001**
White British	48 (21.5)	99 (39.6)			
Black Caribbean	44 (19.6)	39 (15.6)			
Black African	54 (24.1)	32 (12.8)			
White Other	26 (11.6)	50 (20.0)			
Asian (all)	21 (9.4)	14 (5.6)			
Other	31 (13.8)	16 (6.4)			
Level of education			**65.96**	**4**	**<0.001**
No qualification	37 (17.2)	7 (3.1)			
GCSE/O level	51 (23.7)	23 (10.1)			
A level	31 (14.4)	53 (23.2)			
Vocational/College	52 (24.2)	37 (16.2)			
University or professional qualifications	44 (20.5)	108 (47.4)			
Age, years			t=0.604	472	0.546
Mean (S.D.)	28.8 (9.17)	29.3 (9.97)			

df, degrees of freedom; GCSE, General Certificate of Secondary Education; S.D., standard deviation. Figures in bold indicate *p*<0.05.

More than half of the cases were male (60.4%) and from black or other minority ethnic groups (BME) (74.7%). The majority of the controls were also male (53.5%) and from BME groups (60.1%). Mean age at interview was around 29 years both for cases and controls. As expected, cases were significantly more likely to be from a BME group (p<0.001), and have none or only school leaving qualifications (p<0.001) compared to controls. There was not a significant difference in gender (p=0.143) or age (p=0.546) between cases and controls. These demographic factors were all controlled for in the analysis, either because they differed between cases and controls or because they have previously been shown to be associated with adversity exposure and psychosis.

Association between childhood adversity and psychotic disorder

Table 5.2 presents the prevalence of each type of childhood adversity for psychosis cases and controls along with the ORs of the associations with case status in this subsample. All types of childhood adversity occurred more often among psychosis cases than unaffected controls, though only parental loss and separation reach conventional levels of statistical significance. Also in this subsample the association was slightly stronger in those reporting multiple (OR=2.69) than single adverse events (OR=2.39), and the cumulative effect of childhood adversities was confirmed by a significant linear trend (z=4.41, p<0.001).

Following adjustment for demographic factors, only the associations between parental separation and psychosis remained statistically significant, with parental loss (p=0.064) approaching significance. A significant association was detected between both single (p=0.003) or multiple adversities (p=0.018) and psychosis. These results confirm the previously demonstrated association between childhood adversity and psychosis.

Table 5.2 Prevalence of childhood adversity by psychosis case status in this subsample

Type of childhood adversity	Cases (*N*=224) *n* (%)	Controls (*N*=250) *n* (%)	Unadjusted OR	95% CI	*P* value	Adjusted OR*	95% CI	*P* value
Parental separation	123 (55.4)	88 (35.3)	**2.27**	1.57-3.29	**<0.001**	**1.78**	1.18-2.68	**0.006**
Parental loss	28 (12.7)	16 (6.4)	**2.12**	1.12-4.04	**0.022**	1.96	0.96-3.99	0.064
Physical abuse	47 (21.0)	38 (15.3)	1.47	0.91-2.35	0.111	1.19	0.71-1.99	0.519
Sexual abuse	29 (12.9)	25 (10.1)	1.33	0.75-2.34	0.330	1.37	0.74-2.54	0.316
Institutional care	9 (4.0)	5 (2.0)	2.05	0.68-6.21	0.204	1.40	0.44-4.46	0.564
Disrupted family arrangements	44 (20.6)	29 (13.8)	1.61	0.97-2.70	0.067	1.18	0.67-2.06	0.569
Total adversity								
1	97 (43.3)	78 (31.2)	**2.39**	1.57-3.64	**<0.001**	**2.01**	1.27-3.19	**0.003**
2 or more	60 (26.8)	43 (17.2)	**2.69**	1.64-4.39	**<0.001**	**1.92**	1.12-3.29	**0.018**

*Adjusted for gender, age at interview, ethnicity and level of education. CI, confidence interval. OR, odds ratio.

Association between familial liability and psychotic disorder

Table 5.3 presents the prevalence of each type of familial liability for psychosis cases and unaffected controls along with the ORs of the associations with case status.

All types of familial risk were significantly associated with psychosis in probands. However, after adjusting for demographic confounders, the association between parental mental illness and psychosis caseness fell short of statistical significance, as the confidence interval crosses 1. Psychotic disorders were around 4 times more common in first degree relatives of cases than controls, while more broadly defined mental illness (psychosis, depression, or mania) was almost twice as common. This indicates that familial liability could be considered as a proxy genetic risk factor for psychosis, though it could also indicate the negative environmental effects of living with a first-degree relative who has a serious mental disorder. In both cases familial liability might play a role in the previously demonstrated association between childhood adversity and psychosis.

Table 5.3 Prevalence of familial risk by psychosis case status

Type of familial risk	Cases (*N*=224) *n* (%)	Controls (*N*=250) *n* (%)	Unadjusted OR	95% CI	*P* value	Adjusted OR*	95% CI	*P* value
Family mental illness	94 (42.0)	70 (28.0)	**1.86**	1.27-2.73	**0.002**	**1.76**	1.14-2.70	**0.010**
Family psychosis	38 (17.3)	12 (5.1)	**3.90**	1.98-7.68	**<0.001**	**4.11**	1.94-8.72	**<0.001**
Parental mental illness	65 (29.5)	49 (20.8)	**1.60**	1.04-2.45	**0.031**	1.56	0.97-2.49	0.065
Parental Psychosis	28 (12.8)	8 (3.4)	**4.20**	1.87-9.43	**0.001**	**4.71**	1.90-11.67	**0.001**

*Adjusted for gender, age at interview, ethnicity and level of education. CI, confidence interval. OR, odds ratio. Mental illness refers to psychosis, depression or mania.

Proxy rGE for parental psychopathology and childhood adversity

In order to investigate the presence of a passive gene-environment correlation, I tested if parental psychopathology was also associated with childhood adversity in this sample. Therefore, the reported prevalence of parental mental illness and psychosis by exposure to childhood adversity for cases and controls is presented separately in Table 5.4.

Parental psychopathology was not associated with greater exposure to any type of childhood adversity among cases in this sample. However, parental history of depression, mania or psychosis was more common among controls with, compared with those without, a history of parental separation, physical abuse and multiple adversities. These associations remained significant following adjustment for potential confounders. These results do not confirm the presence of a passive rGE, as a parental history of psychosis was associated with greater odds of psychotic disorder but not with greater exposure to childhood adversity among cases in this sample.

Table 5.4 Association between parental mental illness and childhood adversity in psychosis cases and unaffected controls

Type of parental psychopathology	Childhood adversity Present, *n* (%)	Childhood adversity Absent, *n* (%)	Unadjusted OR	95% CI	*P* value	Adjusted OR	95% CI	*P* value
Parental separation								
Psychosis Cases	N=119	N=98						
Parental mental illness	34 (28.6)	30 (30.6)	0.91	0.50-1.63	0.743	1.02	0.53-1.94	0.955
Parental psychosis	13 (11.1)	14 (14.3)	0.75	0.33-1.68	0.485	1.01	0.40-2.52	0.986
Unaffected controls	N=82	N=153						
Parental mental illness	25 (30.5)	24 (15.7)	**2.36**	1.24-4.47	**0.009**	**2.58**	1.30-5.11	**0.007**
Parental psychosis	5 (6.1)	3 (2.0)	3.25	0.76-13.94	0.113	4.36	0.78-24.43	0.094
Parental loss								
Psychosis Cases	N=26	N=190						
Parental mental illness	10 (38.5)	54 (28.4)	1.57	0.67-3.68	0.296	1.91	0.77-4.73	0.162
Parental psychosis	5 (19.2)	23 (12.2)	1.71	0.59-4.97	0.326	2.23	0.71-6.96	0.167
Unaffected controls	N=16	N=219						
Parental mental illness	2 (12.5)	47 (21.5)	0.52	0.11-2.38	0.402	0.56	1.12-2.65	0.463
Parental psychosis	0 (0.0)	8 (3.6)	-	-	-	-	-	-
Physical abuse								
Psychosis Cases	N=47	N=173						
Parental mental illness	14 (29.8)	51 (29.5)	1.01	0.50-2.05	0.967	1.09	0.52-2.31	0.816

Type of parental psychopathology	Childhood adversity Present, *n* (%)	Childhood adversity Absent, *n* (%)	Unadjusted OR	95% CI	*P* value	Adjusted OR	95% CI	*P* value
Parental psychosis	7 (14.9)	21 (12.3)	1.25	0.50-3.15	0.636	1.42	0.53-3.83	0.487
Unaffected controls	N= 38	N=196						
Parental mental illness	15 (39.5)	34 (17.3)	**3.11**	1.47-6.57	**0.003**	**3.74**	1.68-8.33	**0.001**
Parental psychosis	3 (7.9)	5 (2.55)	3.27	0.75-14.33	0.115	4.54	0.93-22.18	0.061
Sexual abuse								
Psychosis Cases	N=29	N=191						
Parental mental illness	10 (34.5)	55 (28.8)	1.30	0.57-2.98	0.533	1.24	0.53-2.89	0.625
Parental psychosis	2 (7.0)	26 (13.8)	0.46	0.10-2.07	0.315	0.46	0.10-2.11	0.317
Unaffected controls	N=22	N=212						
Parental mental illness	8 (36.4)	41 (19.3)	2.38	0.94-6.06	0.068	1.99	0.71-5.60	0.192
Parental psychosis	2 (9.1)	6 (2.8)	3.43	0.65-18.14	0.146	1.60	0.16-15.57	0.685
Disrupted family arrangements								
Psychosis Cases	N=43	N=167						
Parental mental illness	10 (23.3)	52 (31.1)	0.67	0.31-1.46	0.314	0.74	0.33-1.63	0.451
Parental psychosis	3 (7.0)	25 (15.15)	0.42	0.12-1.46	0.173	0.51	0.14-1.83	0.303
Unaffected controls	N=27	N=173						
Parental mental illness	9 (33.3)	30 (17.3)	2.38	0.98-5.81	0.056	2.53	0.96-6.66	0.059
Parental psychosis	2 (7.4)	2 (1.2)	6.84	0.92-50.76	0.060	4.89	0.61-39.00	0.134

Type of parental psychopathology	Childhood adversity Present, *n* (%)	Childhood adversity Absent, *n* (%)	Unadjusted OR	95% CI	*P* value	Adjusted OR	95% CI	*P* value
Multiple adversities								
Psychosis Cases	N=82	N=82						
Parental mental illness	18 (30.5)	20 (30.3)	1.01	0.47-2.17	0.980	1.53	0.64-3.68	0.340
Parental psychosis	7 (11.9)	10 (15.1)	0.75	0.27-2.13	0.593	1.48	0.44-4.91	0.525
Unaffected controls	N=45	N=130						
Parental mental illness	14 (32.6)	15 (12.5)	**3.51**	1.52-8.09	**0.003**	**3.49**	1.42-8.58	**0.006**
Parental psychosis	3 (7.0)	2 (1.6)	4.57	0.74-38.36	0.102	4.42	0.64-30.39	0.131

*Adjusted for gender, age at interview, ethnicity and level of education. – indicates unable to calculate values due to at least one cell containing a zero value. Mental illness refers to psychosis, depression or mania.

Testing for confounding by parental psychopathology

Given that parental psychosis was shown to be strongly associated with psychosis case status, I investigated whether this form of familial risk could be a confounder in the original associations between childhood adversity and psychotic disorder. As parental separation, parental loss and multiple adversities were the only forms of adversity to be robustly associated with psychotic disorder (see Results section 4.2) I only investigated the impact on these associations.

The original association between parental separation and psychotic disorder (adjusted OR 2.19, 95% CI: 1.51-3.19, p<0.001) slightly increased when further adjusting for parental psychosis (adjusted OR 2.22, 95% CI: 1.52-3.27, p<0.001). However, the original association between parental loss and psychotic disorder (adjusted OR 2.04, 95% CI: 1.51-3.19, p=0.039) fell short of statistical significance after adjusting for parental psychosis (adjusted OR 1.85, 95% CI: 0.95-3.59, p=0.070). Reports of 2 or more childhood adversities remained significantly associated with psychosis even after adjusting for parental psychosis (adjusted OR 2.53, 95% CI: 1.53-4.18, p<0.001).

Interaction between familial liability and childhood adversity in psychosis onset

The associations between each combination of childhood adversity and family and parental mental illness and psychotic disorder along with the results of the interaction analyses are presented in Table 5.5.

Associations were evident between parental separation and multiple adversities with psychotic disorder regardless of whether or not participants had a family or parental history of mental illness. There was a trend for associations between physical abuse, sexual abuse, disrupted family arrangements and psychosis to be stronger amongst those with no familial liability for mental illness. However, there was no evidence of a positive additive interaction between these forms of childhood adversity and family history of mental illness. Only for parental loss and familial liability there was suggestive evidence of

departure from additivity (namely a stronger association with psychotic disorder for individuals with both a family psychiatric history and parental loss) but this failed to reach statistical significance.

Table 5.5 The synergistic effects of childhood adversity and familial liability to mental illness on the presence of psychotic disorder

	Association with psychotic disorder					
Combination of risk factors	**Unadjusted OR**	**95% CI**	***P* value**	**Adjusted* OR**	**95% CI**	***P* value**
Parental Separation (PS)						
No PS and no family mental illness (FMI)	[reference]	-	-	[reference]	-	-
PS only (FMI absent)	**3.09**	2.02-4.72	**<0.001**	**4.14**	2.19-7.81	**<0.001**
FMI only (PS absent)	**1.90**	1.13-3.20	**0.015**	**2.25**	1.11-4.54	**0.024**
Both PS and FMI present	**2.33**	1.38-3.93	**0.002**	**2.20**	1.09-4.44	**0.028**
	ICR: -1.66, 95% CI -3.48 to 0.15, p=0.072			ICR: -3.18, 95% CI -6.33 to 0.04, p=0.047		
No PS and no parental mental illness (PMI)	[reference]	-	-	[reference]	-	-
PS only (PMI absent)	**2.86**	1.92-4.26	**<0.001**	**3.75**	2.09-6.75	**<0.001**
PMI only (PS absent)	**1.88**	1.03-3.41	**0.039**	**2.36**	1.04-5.36	**0.040**
Both PS and PMI present	**2.04**	1.14-3.64	**0.016**	1.62	0.75-3.51	0.224
	ICR: -1.70, 95% CI -3.53 to 0.14, p=0.069			ICR: -3.50, 95% CI -6.60 to 0.40, p=0.027		
Parental loss (PL)						
No PL and no family mental illness (FMI)	[reference]	-	-	[reference]	-	-
PL only (FMI absent)	1.53	0.71-3.27	0.276	0.92	0.31-2.80	0.896
FMI only (PL absent)	1.20	0.81-1.78	0.354	1.12	0.67-1.89	0.664
Both PL and FMI present	**3.82**	1.24-11.73	**0.019**	2.57	0.70-9.36	0.153

	Association with psychotic disorder					
Combination of risk factors	**Unadjusted OR**	**95% CI**	***P* value**	**Adjusted* OR**	**95% CI**	***P* value**
	ICR: 2.09, 95% CI -2.29 to 6.47, p=0.350			ICR: 1.52, 95% CI -1.90 to 4.93, p=0.384		
No PL and no parental mental illness (PMI)	[reference]	-	-	[reference]	-	-
PL only (PMI absent)	1.63	0.81-3.25	0.170	0.78	0.29-2.12	0.631
PMI only (PL absent)	1.14	0.73-1.76	0.566	0.89	0.49-1.61	0.693
Both PL and PMI present	**4.95**	1.07-22.88	**0.041**	4.85	0.91-25.64	0.063
	ICR: 3.18, 95% CI -4.43 to 10.80, p=0.412			ICR: 4.18, 95% CI -3.88 to 12.25, p=0.309		
Physical abuse (PA)						
No PA and no family mental illness (FMI)	[reference]	-	-	[reference]	-	-
PA only (FMI absent)	**2.53**	1.43-4.48	**0.001**	1.69	0.74-3.88	0.212
FMI only (PA absent)	**1.63**	1.07-2.48	**0.023**	1.59	0.90-2.82	0.113
Both PA and FMI present	1.18	0.61-2.30	0.622	0.80	0.34-1.91	0.617
	ICR: -1.97, 95% CI -3.74 to 0.21, p=0.028			ICR: -1.48, 95% CI -3.29 to 0.33, p=0.109		
No PA and no parental mental illness (PMI)	[reference]	-	-	[reference]	-	-
PA only (PMI absent)	**2.28**	1.34-3.86	**0.002**	1.53	0.71-3.30	0.280
PMI only (PA absent)	1.61	0.99-2.60	0.054	1.48	0.76-2.86	0.250
Both PA and PMI present	1.00	0.47-2.13	0.999	0.67	0.26-1.76	0.419
	ICR: -1.88, 95% CI -3.49 to -0.27, p=0.022			ICR: -1.33, 95% CI -3.00 to 0.34, p=0.118		

	Association with psychotic disorder					
Combination of risk factors	**Unadjusted OR**	**95% CI**	***P* value**	**Adjusted* OR**	**95% CI**	***P* value**
Sexual abuse (SA)						
No SA and no family mental illness (FMI)	[reference]	-	-	[reference]	-	-
SA only (FMI absent)	1.73	0.90-3.33	0.101	2.32	0.87-6.20	0.092
FMI only (SA absent)	1.41	0.95-2.11	0.091	1.33	0.78-2,28	0.298
Both SA and FMI present	1.19	0.54-2.66	0.663	1.33	0.46-3.81	0.596
	ICR: -0.95, 95% CI -2.49 to 0.60, p=0.231			ICR: -1.32, 95% CI -4.03 to 1.38, p=0.337		
No SA and no parental mental illness (PMI)	[reference]	-	-	[reference]	-	-
SA only (PMI absent)	1.52	0.83-2.76	0.172	2.30	0.96-5.51	0.062
PMI only (SA absent)	1.31	0.84-2.06	0.238	1.27	0.69-2.34	0.434
Both SA and PMI present	1.22	0.47-3.17	0.678	0.93	0.26-3.31	0.908
	ICR: -0.61, 95% CI -2.16 to -0.94, p=0.444			ICR: -1.64, 95% CI -4.09 to 0.80, p=0.188		
Disrupted family arrangements (FA)						
No FA and no family mental illness (FMI)	[reference]	-	-	[reference]	-	-
FA only (FMI absent)	**2.08**	1.17-3.73	**0.013**	1.93	0.91-4.09	0.087
FMI only (FA absent)	**1.67**	1.07-2.59	**0.022**	1.61	0.93-2.80	0.091
Both FA and FMI present	1.26	0.55-2.88	0.578	0.81	0.27-2.44	0.705
	ICR: -1.49, 95% CI -3.21 to 0.23, p=0.089			ICR:-1.73, 95% CI 3.66 to 0.19, p=0.078		
No FA and no parental mental illness (PMI)	[reference]	-	-	[reference]	-	-

	Association with psychotic disorder					
Combination of risk factors	**Unadjusted OR**	**95% CI**	***P* value**	**Adjusted* OR**	**95% CI**	***P* value**
FA only (PMI absent)	**1.97**	1.13-3.44	**0.016**	1.81	0.88-3.71	0.104
PMI only (FA absent)	1.64	0.99-2.70	0.053	1.33	0.72-2.47	0.360
Both FA and PMI present	1.05	0.42-2.65	0.918	0.48	0.13-1.73	0.264
	ICR: -1.56, 95% CI -3.22 to 0.10, p=0.065			ICR: -1.66, 95% CI -3.35 to 0.03, p=0.054		
Multiple adversities (MA)						
No MA and no family mental illness (FMI)	[reference]	-	-	[reference]	-	-
MA only (FMI absent)	**4.04**	2.30-7.10	**<0.001**	**2.95**	1.55-5.60	**0.001**
FMI only (MA absent)	**2.99**	1.57-5.72	**0.001**	**2.79**	1.37-5.65	**0.004**
Both MA and FMI present	**3.45**	1.74-6.86	**<0.001**	**2.44**	1.16-5.15	**0.019**
	ICR: -2.58, 95% CI -6.04 to 0.87, p=0.142			ICR: -2.29, 95% CI -5.34 to 0.76, p=0.141		
No MA and no parental mental illness (PMI)	[reference]	-	-	[reference]	-	-
MA only (PMI absent)	**3.83**	2.26-6.50	**<0.001**	**2.75**	1.51-5.02	**0.001**
PMI only (MA absent)	**2.47**	1.18-5.17	**0.016**	**2.21**	1.00-4.89	**0.049**
Both MA and PMI present	**2.38**	1.11-5.12	**0.026**	1.80	0.80-4.08	0.156
	ICR: -2.92, 95% CI -6.03 to 0.13, p=0.066			ICR: -2.16, 95% CI -4.87 to 0.55, p=0.118		

*Adjusted for gender, age at interview, ethnicity and level of education. CI, confidence interval. ICR, interaction contrast ratio. OR, odds ratio. Mental illness refers to psychosis, depression or mania.

Discussion

In this section I investigated the role of different forms of childhood adversity and familial liability to mental illness, as well as the interaction between them, in relation to the presence of psychotic disorder. The strongest associations between childhood adversity and psychotic disorder were found for parental separation and multiple adversities in keeping with previous findings from an overlapping geographical area (Fisher et al., 2010; Morgan et al., 2007). Moreover, within this sample, family history of mental illness was unsurprisingly a significant risk factor for psychotic disorder. Indeed, a history of psychosis in at least one parent was 4 times more common among participants with psychotic disorder than community controls. These findings are in line with previous studies suggesting that subclinical psychotic experiences as well as clinical psychosis represent the developmental expression of genetic and environmental liability to psychosis (Cougnard et al., 2007; Lataster et al., 2009), with a much larger association in monozygotic than in dizygotic twins.

There was a smaller but significant association between current or past mental illness (psychosis, depression, or mania) in a first degree relative and clinical presentation of psychosis in this sample. This is consistent with studies suggesting that there is a partial genetic overlap between schizophrenia and affective disorders (Cardno et al., 2002; Cross-Disorder Group of the Psychiatric Genetics Consortium, 2013).

However, an association between parental history of psychosis and childhood adversity among the psychosis cases was not found. Moreover, in keeping with these findings, controlling for parental history of psychosis only resulted in a small reduction in the strength of the association between parental separation and psychotic disorder, as well as in the cumulative effect of childhood adversities on the presence of psychosis. Therefore, results could not confirm the presence of a potential passive gene-environment correlation, in which parents pass on both a genetic liability to psychosis and create an abusive environment, which has been reported in a previous study (Fisher et al., 2014)

though this was specifically for maternal physical abuse. An adoption design would be required to exclude fully the possibility of a passive rGE (Plomin et al., 1977) operating in this association but suitable samples are rarely available. Unfortunately, it was not possible in the current study to explore other forms of rGE, namely evocative or active, e.g., the child's genetic propensities eliciting harsher methods of physical punishment or making them more likely to select solitary or other risky environments (Plomin et al., 1977).

Moreover, there was no evidence for additive interactions between parental separation, physical abuse or sexual abuse, disrupted family arrangements, multiple adversities in childhood and family psychiatric history in relation to the presence of psychotic disorder. This could suggest that these forms of childhood adversity may be associated with psychotic disorder independently of proxy genetic risk but might also reflect a lack of statistical power in this sample. These findings are in line with previous studies reporting that the effect of childhood trauma on later experience of psychotic symptoms was independent of proxy genetic liability to psychosis (Arseneault et al., 2011; Wigman et al., 2012; Fisher et al., 2014). Though my findings suggest that this may not be the case for parental loss. Overall, these results suggest that biological and environmental risk factors are both important in the aetiology of psychosis but the effects of some forms of childhood adversity act largely independently of pre-existing genetic liability to increase risk of psychosis.

Results section 5.2

Family history, childhood adversity and one-year outcomes

Association between familial liability and course of psychosis

Table 5.6 presents the prevalence of each type of familial liability for psychosis by one-year follow-up outcomes along with the ORs of the associations between these factors. All types of familial risk were significantly associated with being in a steady relationship at follow-up. No association was found for family psychiatry history with length of hospital stay over the follow-up period. There was a trend for those with a family history of mental illness to be more compliant with medications at one-year from first contact with mental health services though this association only became statistically significant after adjustment for DUP and baseline compliance (p=0.049).

Table 5.7 shows the associations between familial risk and clinical and social/vocational functioning at one-year follow-up amongst psychosis cases. All types of familial risk were significantly associated with increased scores on the GAF-disability scale, indicating improved functioning, after adjustment for DUP and baseline GAF-disability score. Thus familial liability might play a role in the previously demonstrated associations between physical abuse and relationship status and between parental loss and social/vocational functioning. However, no association was found between familial liability and GAF-symptoms scores at one year. This indicates that familial liability did not impact on the course of psychotic symptoms in this sample.

Table 5.6 Association between familial risk and one-year follow-up outcomes in psychosis cases

Type of familial risk								
Relationship status	**In a relationship n (%)**	**Not in a relationship n (%)**	**Unadjusted OR**	**95% CI**	***P* value**	**Adjusted OR***	**95% CI**	***P* value**
Family mental illness	33 (57.9)	48 (37.21)	**0.43**	0.23-0.81	**0.009**	**0.23**	0.09-0.54	**0.001**
Family psychosis	16 (28.6)	19 (15.1)	**0.44**	0.21-0.95	**0.036**	**0.25**	0.10-0.64	**0.004**
Parental mental illness	24 (43.7)	31 (24.4)	**0.42**	0.21-0.81	**0.010**	**0.42**	0.21-0.81	**0.010**
Parental Psychosis	14 (25.4)	12 (9.6)	**0.31**	0.13-0.73	**0.007**	**0.28**	0.12-0.66	**0.004**
Hospital admission days	**Less than 49 days n (%)**	**49 days or more n (%)**						
Family mental illness	45 (47.9)	36 (38.7)	0.69	0.39-1.23	0.207	**0.32**	0.13-0.80	**0.015**
Family psychosis	20 (21.3)	15 (16.8)	0.75	0.35-1.58	0.448	0.53	0.18-1.57	0.251
Parental mental illness	33 (35.5)	23 (25.6)	0.62	0.33-1.18	0.146	0.28	0.10-0.76	0.013
Parental Psychosis	33 (35.5)	23 (25.6)	0.89	0.39-2.05	0.786	0.39	0.11-1.30	0.125
Compliance with medications	**Compliant n (%)**	**Non-compliant n (%)**						
Family mental illness	55 (48.2)	18 (32.7)	0.52	0.27-1.02	0.058	**0.44**	0.20-1.00	**0.049**
Family psychosis	20 (18.0)	10 (18.5)	0.75	0.35-1.60	0.458	0.81	0.30-2.17	0.075
Parental mental illness	38 (33.9)	12 (22.6)	0.75	0.35-1.60	0.458	0.44	0.18-1.07	0.071
Parental Psychosis	15 (13.6)	7 (13.2)	0.96	0.37-2.53	0.940	0.69	0.23-2.10	0.518

*Adjusted for baseline relationship status (for relationship status at follow-up); duration of untreated psychosis and Global Assessment of Functioning symptom scores (for hospital admission days); duration of untreated psychosis and compliance with medications at baseline (for compliance at 12 months). CI, confidence interval. OR, odds ratio. Mental illness refers to psychosis, depression or mania.

Table 5.7 Association between familial risk and clinical and social/vocational functioning at one-year follow-up in psychosis cases

Type of familial risk	Absent Mean (S.D.)	Present Mean (S.D.)	B	95% CI	*P* value	Adjusted B*	95% CI	*P* value
GAF symptoms								
Family mental illness	59.2 (20.30)	58.3 (20.03)	-0.90	-6.96-5.16	0.770	7.05	-1.82-15.93	0.118
Family psychosis	58.8 (20.35)	59.6 (19.84)	0.77	-6.80-8.34	0.842	6.05	-4.89-16.99	0.274
Parental mental illness	58.9 (20.04)	60.0 (20.00)	1.13	-5.43-7.69	0.734	5.19	-4.48-14.86	0.288
Parental Psychosis	59.2 (19.66)	60.8 (21.69)	1.67	-6.87-10.20	0.700	5.77	-6.32-17.86	0.345
GAF disability								
Family mental illness	54.9 (19.23)	57.0 (21.37)	2.04	-4.02-8.10	0.508	**13.31**	4.98-21.64	**0.002**
Family psychosis	55.7 (19.84)	57.8 (21.54)	2.03	-5.52-9.58	0.597	**10.63**	0.19-21.06	**0.046**
Parental mental illness	54.6 (19.34)	59.9 (21.26)	5.26	-1.27-11.79	0.114	**11.58**	2.42-20.76	**0.014**
Parental Psychosis	55.5 (19.46)	62.0 (22.37)	6.49	-2.01-15.00	0.134	**11.97**	0.47-23.47	**0.042**

*Adjusted for duration of untreated psychosis and baseline Global Assessment of Functioning Scale (Symptoms or Disability as appropriate). B, regression coefficient; CI, confidence interval; GAF, Global Assessment of Functioning scale. Mental illness refers to psychosis, depression or mania.

Therefore, I investigated whether parental psychosis could be a confounder in the original associations between childhood adversity and one-year outcomes. As physical abuse and parental loss were the only forms of adversity to be robustly associated with relationship status and social/vocational functioning respectively (see section 4.2, chapter 4) I only investigated the impact on these associations. Specifically, physical abuse was associated with not being in a relationship at follow-up, while parental loss was associated with better social functioning (corresponding to a higher GAF-disability score) at one-year.

The original association between physical abuse and relationship status at one year (adjusted OR 2.82, 95% CI: 1.07-7.43, p=0.035) slightly reduced and fell short of statistical significance (adjusted OR 2.69, 95% CI: 0.87-8.34, p=0.087) following adjustment for parental psychosis. However, the original association between parental loss and GAF-disability (adjusted B 22.64, 95% CI: 11.03-34.28, p<0.001) increased when further adjusting for parental psychosis (adjusted B 26.56, 95% CI: 14.64-38.47, p<0.001).

Interaction between familial liability and childhood adversity in psychosis outcomes

Table 5.8 presents the associations between each combination of childhood adversity and family and parental mental illness and one-year outcomes along with the results of the interaction analyses. Associations were evident between parental separation and length of hospitalisation in participants with no family or parental history of mental illness (OR=3.08). There was a trend for associations between parental separation and non-compliance with medications at 12 months to be stronger amongst those with no familial (p=0.095) or parental (p=0.110) liability for mental illness. In the adjusted model, parental separation remained significantly associated with days spent in hospital over the first year of illness in participants with no family history of mental illness, with a five-fold increased odds of staying longer in hospital (more than 49 days) compared to those who did not report parental separation during childhood (Adjusted OR=5.04).

Table 5.8 The synergistic effects of childhood adversity and familial liability to mental illness on one-year psychosis outcomes

	Association with psychosis outcomes					
Combination of risk factors	**Unadjusted OR**	**95% CI**	***P* value**	**Adjusted* OR**	**95% CI**	***P* value**
Parental Separation (PS)	**Compliance with medications at 12 months**					
No PS and no family mental illness (FMI)	[reference]	-	-	[reference]	-	-
PS only (FMI absent)	1.85	0.90-3.84	0.095	2.54	0.97-6.67	0.059
FMI only (PS absent)	0.59	0.22-1.58	0.296	0.52	0.16-1.70	0.277
Both PS and FMI present	0.74	0.29-1.88	0.527	0.86	0.26-2.80	0.797
	ICR: -0.70, 95% CI -2.18 to 0.76, p=0.334			ICR: -1.20, 95% CI -3.64 to 1.24, p=0.335		
No PS and no parental mental illness (PMI)	[reference]	-	-	[reference]	-	-
PS only (PMI absent)	1.73	0.88-3.38	0.110	**2.67**	1.18-6.07	**0.019**
PMI only (PS absent)	0.55	0.18-1.69	0.299	0.93	0.32-2.72	0.893
Both PS and PMI present	0.82	0.29-2.27	0.698	1.27	0.43-3.74	0.662
	ICR: -0.46, 95% CI -1.84 to 0.92, p=0.510			ICR: -1.33, 95% CI -3.81 to 1.15, p=0.294		
Parental Separation (PS)	**Hospital admission days**					
No PS and no family mental illness (FMI)	[reference]	-	-	[reference]	-	-
PS only (FMI absent)	**3.08**	1.57-6.02	**0.001**	**5.04**	1.59-15.94	**0.006**
FMI only (PS absent)	1.51	0.66-3.46	0.334	1.05	0.29-3.73	0.944
Both PS and FMI present	1.27	0.57-2.84	0.550	0.77	0.21-2.86	0.700

Combination of risk factors	Unadjusted OR	95% CI	*P* value	Adjusted* OR	95% CI	*P* value
	ICR:-2.30, 95% CI -4.80 to 0.19, p=0.070			ICR: -4.31, 95% CI -10.45 to 1.82, p=0.168		
No PS and no parental mental illness (PMI)	[reference]	-	-	[reference]	-	-
PS only (PMI absent)	**2.65**	1.43-4.90	**0.002**	2.69	0.96-7.49	0.059
PMI only (PS absent)	1.26	0.50-3.17	0.619	0.33	0.07-1.53	0.158
Both PS and PMI present	0.93	0.39-2.24	0.872	0.65	0.17-2.47	0.530
	ICR: -1.98, 95% CI -4.11 to 0.14, p=0.068			ICR: -1.36, 95% CI -4.12 to 1.38, p=0.329		
Physical abuse (PA)				**Relationship status at follow-up**		
No PA and no family mental illness (FMI)	[reference]	-	-	[reference]	-	-
PA only (FMI absent)	1.32	0.52-3.34	0.560	2.29	0.66-7.95	0.192
FMI only (PA absent)	**0.40**	0.21-0.76	**0.006**	**0.21**	0.09-0.51	**0.001**
Both PA and FMI present	0.83	0.27-2.52	0.739	0.71	0.14-3.52	0.678
	ICR: 0.11, 95% CI -1.33 to 1.56, p=0.880			ICR: -0.78 , 95% CI -3.74 to 2.16, p=0.600		
No PA and no parental mental illness (PMI)	[reference]	-	-	[reference]	-	-
PA only (PMI absent)	1.53	0.65-3.61	0.332	3.01	0.91-9.99	0.070
PMI only (PA absent)	**0.41**	0.20-0.84	**0.015**	**0.27**	0.11-0.67	**0.005**
Both PA and PMI present	0.72	0.20-2.54	0.606	0.64	0.12-3.40	0.603
	ICR:-0.22, 95% CI -1.77 to 1.33, p=0.778			ICR: -1.65, 95% CI -5.35 to 2.05, p=0.381		

*Adjusted for baseline relationship status (for relationship status at follow-up), duration of untreated psychosis and Global Assessment of Functioning symptom scores (for hospital admission days); duration of untreated psychosis and compliance with medications at baseline (for compliance with medications at 12 months). CI, confidence interval. OR, odds ratio. Mental illness refers to psychosis, depression or mania.

Furthermore, the association between parental separation and non-compliance with medications at 12 months in participants with no parental history of mental illness became significant after adjusting for compliance with medication at baseline and duration of untreated psychosis ($p=0.019$). There was a trend for associations between physical abuse and not being in a steady relationship at follow-up amongst those with no familial liability for mental illness. However, participants with a history of mental illness in first-degree relatives but no history of physical abuse were significantly more likely to be in a relationship at follow-up (all $p<0.05$). However, there was no evidence of a positive additive interaction between these forms of childhood adversity and family history of mental illness.

Table 5.9 shows results of the interplay between parental loss and familial liability to mental illness on clinical and social/vocational functioning at one-year follow-up. There was a trend for associations between parental loss and GAF-disability scores at 12 months to be stronger amongst those with no familial liability for mental illness.

Table 5.9 The synergistic effects of parental loss and familial liability to mental illness on clinical and social/vocational functioning at one-year follow-up

	Association with one-year clinical and social functioning					
Combination of risk factors	**Unadjusted B**	**95% CI**	***P* value**	**Adjusted* B**	**95% CI**	***P* value**
Parental loss (PL)			**GAF symptoms**			
No PL and no family mental illness (FMI)	[reference]	-	-	[reference]	-	-
PL only (FMI absent)	6.71	-8.06-21.49	0.371	12.45	-7.88-32.77	0.226
FMI only (PL absent)	-1.31	-7.96-5.33	0.697	4.00	-5.32-13.33	0.395
PL x FMI	-1.31	-20.27-17.64	0.891	8.83	-17.29-34.96	0.503
No PL and no parental mental illness (PMI)	[reference]	-	-	[reference]	-	-
PL only (PMI absent)	2.56	-9.89-15.01	0.685	12.82	-5.26-30.92	0.162
PMI only (PL absent)	-1.61	-8.77-5.56	0.659	0.71	-9.27-10.67	0.887
PL x PMI	13.94	-5.14-33.02	0.151	17.18	-9.03-43.40	0.196
Parental loss (PL)			**GAF disability**			
No PL and no family mental illness (FMI)	[reference]	-	-	[reference]	-	-
PL only (FMI absent)	14.37	-0.26-29.00	0.054	**22.59**	3.86-41.31	**0.019**
FMI only (PL absent)	2.37	-4.21-8.94	0.478	**11.79**	3.24-20.33	**0.007**
PL x FMI	-11.69	-30.45-7.07	0.220	-4.30	-28.21-19.61	0.721

	Association with one-year clinical and social functioning					
Combination of risk factors	**Unadjusted B**	**95% CI**	***P* value**	**Adjusted* B**	**95% CI**	***P* value**
No PL and no parental mental illness (PMI)	[reference]	-	-	[reference]	-	-
PL only (PMI absent)	9.95	-2.43-22.33	0.114	**21.97**	5.37-38.56	**0.010**
PMI only (PL absent)	3.94	-3.18-11.06	0.276	8.34	-0.82-17.50	0.074
PL x PMI	0.67	-18.30-19.63	0.945	6.09	-17.89-30.06	0.615

*Adjusted for duration of untreated psychosis and baseline Global Assessment of Functioning Scale (symptoms and disability). B, regression coefficient; CI, confidence interval; GAF, Global Assessment of Functioning scale. Mental illness refers to psychosis, depression or mania.

After adjusting for baseline GAF scores and DUP, the association between parental loss and GAF-disability scores at 12 months amongst those with no familial (p=0.019) or parental (p=0.010) liability for mental illness became significant. Moreover, a significant association between family mental illness and GAF-disability scores was found in those with no history of parental loss (p=0.007). However, there were no interaction effects between parental loss and family history of mental illness on GAF disability scores at follow-up.

Discussion

Although several studies have suggested that the course and severity of psychosis is affected by the presence of a family history of psychosis (Kendler et al., 1997; Malaspina et al., 1998) this was not the case in this study. A recent systematic review and meta-analysis on the effects of family history of psychosis on occupational and social outcome in schizophrenia (Käkelä et al., 2014) showed a small but statistically significant association with long-term occupational and global outcome in patients with schizophrenia. Results from this study did not confirm such association for the short-term outcomes: family history of psychosis was not associated with poorer outcomes at one-year from illness onset. These findings are in line with several previous studies, which found that patients with positive family history did not differ from patients with no affected relatives in terms of psychosis symptoms (Baron et al., 1982; Malaspina et al., 2000; van Os et al., 1997). However, another study found that familial loading for psychotic disorder predicted persistent negative symptoms and lower likelihood to recover over the follow-up period, and was also associated with more time hospitalised, and more social disability at 4-year follow-up (Verdoux et al, 1996). In another study (Wieselgren & Lindström, 1996), patients with a family history had a poorer outcome at one-year follow-up compared with those without liability, but this difference was not seen at five-year follow-up.

Findings from this chapter suggest that familial liability to mental illness is associated with being in a relationship at follow-up and better social/vocational functioning at one year compared to those without family history of mental illness. Therefore, it might be that different follow-up times bring different results (Käkelä et al., 2014). It may also be that psychosis patients with a positive family history are more likely to maintain and create independent living for themselves, to develop social skills and increased initiatives to contact other people (Hultman et al., 1997), as mechanism to compensate the lack of care and support of a family copying with mental illness.

Furthermore, in line with the baseline results, childhood adversity and family risk did not synergistically interact on the course of psychotic disorder. In contrast, a cohort study showed a genetic and environmental contribution on the course of subclinical psychosis: experiencing childhood trauma and having a monozygotic co-twin with persistent subclinical psychosis symptoms significantly predicted the presence and an increase of psychotic experiences in the other co-twin over two years (Wigman et al., 2011). However, it is not possible to compare the current findings with similar clinical samples as there are no previous studies that investigated this GxE interplay on first-episode psychosis outcomes.

Strengths and limitations

To my knowledge, this is the first study to explore the interplay between familial liability and various forms of childhood adversity in relation to the presence of psychotic disorder and its course over the first year since contact with mental health services. This extends a previous report that focused exclusively on the interplay between family psychiatric history and maternal physical abuse and presence of psychosis (Fisher et al., 2014).

The current study has several advantages, such as the inclusion of a sample of patients that had recently presented to mental health services with a psychotic disorder, thus extending previous reports that only examined psychotic

symptoms or probable psychosis in the general population (Arseneault et al., 2011; Alemany et al., 2013; Heins et al., 2011; Pfeifer et al., 2010; Wigman et al., 2012). The proportion of cases reporting a first degree relative with psychosis in this sample was 17.3%, compared to 5.1% the control group, which is also within the range of existing studies (Fisher et al., 2014; Tienari et al., 2003). Additionally, as already mentioned in the previous chapter, I used a standardised measure of adverse childhood experiences (Bifulco et al., 2005) and I was able to control for the potentially confounding effects of a range of demographic and clinical characteristics. Furthermore, several other past studies that have examined treatment outcome as a function of family history did not focus on first-episode patients (e.g., Chanpattana & Chakrabhand, 2001; Feldman et al., 2001; Ganev, 2000; Nimgaonkar et al., 1988; Silverman et al., 1987), therefore this study represents a novel topic of investigation.

However, I had only 25% power to detect the 5% difference in proportions exposed to parental separation among individuals with a family history (n=162), compared with 100% power to detect the 27% difference in those without a family psychiatric history (n=308). Thus, I did not have enough power to test for interactions between childhood adversity and family psychiatric history in the association with psychotic disorder. Therefore, these findings should be interpreted with caution and need to be replicated in larger samples.

Finally, in this study I used familial psychopathology as a proxy for genetic liability which may not have captured all of the relevant genetic influences in the participants (Farmer et al., 1990). For instance, negative family history can include undeclared or unknown positive family history of mental illness. The interviews were supplemented with information obtained from clinical records (for the cases) but there still may have been cases in the families that were missed. It is also possible that family members have a genetic propensity to developing mental health problems but this has not (yet) been phenotypically expressed. Family psychiatric history also captures familial effects of non-genetic

origin (van Os et al., 2008). However, the shared familial (non-genetic) component of schizophrenia risk is estimated to account for just a small proportion of the overall trait variance (4.5% to 11%; Lichtenstein et al., 2009).

I am aware of the fact that family psychiatric history alone cannot fully test gene-environment correlations (rGE) and gene-environment (GxE) interactions but I do believe it is one strategy that allows us to get some purchase on gene-environment interplay. A number of published studies have examined rGE and GxE using such indirect measures of genetic risk (e.g., Carter et al., 2002; Clarke et al., 2009; Fisher et al., 2014; Wigman et al., 2012). This proxy genetic approach is considered useful given that a large number of genes, mainly of very small effect, are involved in genetic susceptibility to psychosis (Sullivan et al., 2012), rendering single candidate gene approaches extremely difficult.

Family history of psychosis has the advantage of a much larger effect size but it may reflect both genetic risk and some aspects of the environment in which individuals are brought up (van Os et al., 2008) though some studies suggest that this shared environmental component is likely to be fairly minimal (Lichtenstein et al., 2009). Therefore, I considered family psychiatric history as first step to exploring gene-environment interplay which could be supplemented by measured gene by environment interactions (see subsequent chapters).

There has been a shift in psychiatric genetics towards using polygenic risk scores rather than candidate genes to index genetic risk for mental illness which could be used to explore GxE in smaller samples than required for candidate gene by environment analysis. However, Jaffee and Price (2012) have warned that this may not necessarily be any more helpful than using family history in understanding the mechanisms underlying gene-environment interplay because polygenic risk scores aggregate information across thousands of SNPs and thus in essence provide a (more expensive) “black box” genetic risk estimate than family psychiatric history.

Consequently, the impact of familial liability in this sample might have been underestimated and replication using more comprehensive molecular measures of genetic risk is needed. However, very large samples are required to identify sufficient common SNPs to explain a reasonable proportion of the genetic architecture of psychotic disorders and polygenic risk scores may not get us closer to understanding the specific mechanisms involved in GxE (Jaffee & Price, 2012). A recent study showed that the excess risk of offspring schizophrenia in families affected by psychotic, bipolar affective or other psychiatric disorder is essentially unchanged when SNP-based variation is taken into account (Agerbo et al., 2012). This provides some reassurance that the data obtained in the current study on psychiatric disorder in first degree relatives had an adequate degree of accuracy.

Nonetheless, future research using larger clinical samples and exploring whether measured genes moderate the impact of childhood adversity on the onset and course of psychotic disorders would be beneficial. More sensitive measures of genetic risk (Iyegbe et al., 2014) will be used in further investigations in Chapter 6 and 7 of this thesis.

Clinical implications and further directions of research

These results have potential implications for both clinical and research practice. Given that several forms of childhood adversity have been shown in the present study to be associated with psychotic disorder regardless of the presence or absence of familial liability, preventing trauma occurring or helping children to cope better in the aftermath of exposure could potentially help to prevent the onset of psychosis. Indeed, as recently shown by Kelleher et al. (2013), the cessation of exposure to traumatic experiences might lead to a reduction in the incidence of psychotic experiences. Therefore, interventions focused on stopping childhood adversity or dealing with its consequences might have an impact not only on preventing the onset of psychosis but also on its longer-term course. Furthermore, research has shown that if the caregiver is perceived as

unavailable, unresponsive and insensitive, this could lead to the development of an insecure attachment style in the child and to the child experiencing difficulties in relating to others (Mathews et al., 2014). Therefore, interventions focused on helping parents with psychosis and other severe mental health problems to develop better relationships with their families and/or providing family education and support could improve their children's attachment relationships and in turn, help children develop more positive relationships with others in adulthood (Mathews et al., 2014). Increased social networks and perceived support may reduce the likelihood of such children developing psychosis (Gayer-Anderson & Morgan, 2013; Matthews et al., 2015) and warrant further investigation.

Synthesis of chapter 5

Psychotic disorders were around 4 times more common in first degree relatives of cases than controls. No evidence of a gene-environment correlation for presence of psychotic disorder was found, such that participants with a parental history of psychosis were not more likely to report exposure to childhood adversity. Furthermore, there was no evidence that childhood adversity and familial liability combined synergistically to increase odds of psychosis beyond the effect of each individually.

In line with baseline results, no evidence was found for familial by childhood adversity interactions on the course of psychosis. The main effect of parental separation on length of hospitalisation and medication adherence at one year in participants with no family or parental history of mental illness was confirmed. There was a non-significant trend for a greater association with not being in a steady relationship amongst those who reported exposure to childhood physical abuse but no parental mental illness.

Therefore, these results do not support the hypothesis that family psychiatric history amplifies the effect of childhood adversity on odds of psychosis and on one-year outcomes. Overall, these findings suggest that biological and environmental risk factors are both important in the aetiology of psychosis and that the effects of some forms of childhood adversity may act largely independently of pre-existing familial (possibly genetic) liability to increase risk of psychosis and its outcomes. Though further investigations are warranted using larger samples.

The impact of specific genetic variations, using a direct molecular measure, on the associations between these adverse childhood experiences and psychosis will be explored in Chapter 6.

CHAPTER 6 – Synergistic effect of childhood adversity and genotype in the onset of psychosis and one year outcomes

Aims of this chapter

The main purpose of this chapter is to conduct an investigation into the potential interaction between childhood adversity and biologically plausible candidate genes in the onset of adult psychosis. As for Chapters 4 and 5, this study utilises data from the GAP first-episode psychosis case-control study dataset and one year follow-up.

The specific aims are as follows:

1. To test if each of the selected genetic variants are associated with an increased risk of psychotic disorders.
2. Investigate gene-environment correlations between the *COMT*, *AKT1*, and *FKBP5* polymorphisms and types of childhood adversity.
3. Conduct a preliminary test of a genes x exposure to childhood adversity interaction in psychosis using an 'oligogenic risk score' constructed with the selected candidate genes.
4. Explore gene-environment interactions between each of the selected genetic variants and adverse childhood experiences in differentiating between psychosis cases and unaffected controls.
5. Explore gene-environment interactions between the *COMT*, *AKT1*, and *FKBP5* genotypes and adverse childhood experiences on one-year clinical and social outcomes.

Results section 6.1

Genotype, childhood adversity and psychosis onset

COMT Val158Met

Data on childhood adversity and *COMT Val158Met* genotype were available on 250 out of 285 psychosis cases and 201 out of 256 community controls drawn from the GAP study with completed CECA.Q data, with an overall call rate of 85%. Cases with and without *COMT Val158Met* genotype data did not differ in terms of gender (χ^2=0.480, *p*=0.581), age (t=0.266(282), p=0.760), ethnicity (χ^2=14.89, *p*=0.188) and education (χ^2=1.760, *p*=0.787). No differences were found for controls with and without *COMT Val158Met* genotype data in terms of gender (χ^2=0.306, *p*=0.581), age (t=-0.732(252), *p*=0.465), ethnicity (χ^2=14.93, *p*=0.185) and education (χ^2=3.573, *p*=0.467).

In the sample investigated, the majority of cases (n=149, 59.6%) and controls (n=109, 54.2%) were male and the mean age at interview was 29.4 years for cases and 28.9 years for controls. Less than half of the cases (n=61, 24.4%) and controls (n=75, 37.5%) were of White British ethnicity. As expected, cases were more likely to be from a black or other minority group (χ^2=0.264, *p*=0.001), and more likely to have no qualifications or only GCSE or O level qualifications compared to controls (χ^2=62.47, *p*=0.001). No significant differences were found between the psychosis cases and community controls in terms of gender (χ^2=-0.054, *p*=0.292), or age (t=-0.629(df=449), *p*=0.530).

The distribution of the three *COMT* genotypes (*Val/Val*, *Val/Met* and *Met/Met*) are presented in Table 6.1 along with the expected prevalence according to the Hardy-Weinberg Equilibrium (HWE) equation: [where *Val* has a frequency of p and *Met* has a frequency of (1-p), expected genotype frequencies are as follows: *Val/Val*=p^2, *Val/Met*= 2p(1-p) and *Met/Met*=$(1-p)^2$] and the findings of the HWE tests. The results are reported separately for controls and cases, as the distribution of genotypes has a greater likelihood of diverging from equilibrium in the case sample as a consequence of a certain allele or genotype being associated with psychopathology.

Table 6.1 Hardy-Weinberg Equilibrium results for *COMT* genotypes in cases and controls

Group	***Val/Val***	***Val/Met***	***Met/Met***	***HWE***	***Exact***
	n	***n***	***N***	***X^2***	***P***
Controls (N=201)				2.881	0.089
Observed	74	105	22		
Expected	79.61	93.77	27.61		
Cases (N=250)				**4.493**	**0.034**
Observed	96	130	24		
Expected	103.68	114.63	31.68		

HWE, Hardy-Weinberg Equilibrium. *Met*, methionine. *Val*, valine.

The *COMT* genotypes were in Hardy–Weinberg equilibrium amongst controls (χ^2=2.881, *p*=0.089). In the cases the HWE was breached (*p*=0.034). Although, traditionally a *p* value <0.05 was considered to breach the HWE, recent GWAS have suggested a much higher threshold of significance (10^{-4}) before discarding a SNP on the assumption of genotyping error (Wellcome Trust Case Control Consortium, 2007). This was the case, especially when HWE is calculated for a SNP genotyped together with other polymorphisms across different populations. The distribution of the *COMT* genotypes was similar between psychosis cases and controls and this was confirmed by a non-significant result for Cuzick's non-parametric trend test (z=0.46, *p*=0.645).

AKT1 rs2494732

AKT1 rs2494732 genotyping data were obtained on 245 psychosis cases and on 191 controls. This corresponds to an overall call rate of 85%. Cases with and without *AKT1* rs2494732 genotype data did not differ in terms of gender (χ^2=0.420, *p*=0.602), age (t=0.146(282), p=0.884), ethnicity (χ^2=11.97, *p*=0.367) and education (χ^2=1.673, *p*=0.802). No differences were found for controls with

and without *AKT1* rs2494732 genotype data in terms of gender (χ^2=0.108, *p*=0.773), age (t=-0.661(252), *p*=0.509), ethnicity (χ^2=18.21, *p*=0.063) and education (χ^2=3.327, *p*=0.512).

The majority of cases (59.6%) and controls (53.9%) were males. Cases were more likely to be from a black or other minority group (χ^2=28.82, *p*=0.002) and to have no qualification or only GCSE/O levels compared to controls (χ^2=59.95, *p*=0.002). No significant differences were found between the psychosis cases and community controls in terms of gender (χ^2=1.406, *p*=0.243), and age (t=-0.592 (434), *p*=0.156).

Table 6.2 presents the distribution of the three *AKT1* genotypes (*C/C*, *C/T*, *T/T*) along with the expected prevalence according to the HWE equation: [where *C* has a frequency of p and *T* has a frequency of (1-p), expected genotype frequencies are as follows: *C/C* = p^2, *C/T*= 2p(1-p) and *T/T* = $(1-p)^2$] and the findings of the HWE tests.

Table 6.2 Hardy-Weinberg Equilibrium results for *AKT1* genotypes in cases and controls

Group	***C/C***	***C/T***	***T/T***	***HWE***	***Exact***
	n	***n***	***n***	***X^2***	***P***
Controls (N=191)				0.030	0.864
Observed	43	94	54		
Expected	42.41	95.18	53.41		
Cases (N=245)				0.525	0.468
Observed	54	128	63		
Expected	56.83	122.33	65.83		

HWE, Hardy-Weinberg Equilibrium.

The *AKT1* rs2494732 polymorphism allele was in Hardy-Weinberg Equilibrium amongst both cases (χ^2=0.525, *p*=0.468) and controls (χ^2=0.030, *p*=0.864). There

was no significant difference in *AKT1* rs2494732 allelic distribution between cases and controls, and this was confirmed by a non-significant result for Cuzick's non-parametric trend test (z=0.32, p=0.748). Therefore, there was no main effect also of the *AKT1* rs2494732 polymorphism on psychosis in this sample.

FKBP5 rs1360780

Childhood adversity and *FKBP5* rs1360780 genotype data were available on 231 psychosis cases and 191 community controls, with an overall call rate of 79%. Cases with and without *FKBP5* rs1360780 genotype data did not differ in terms of gender (χ^2=0.555, p=0.537), age (t=0.475(282), p=0.635), and education (χ^2=3.326, p=0.508). However, cases with *FKBP5* rs1360780 genotype data were more likely to be black or another minority group (χ^2=20.79, p=0.037) compared to cases not included in these analyses. No differences were found for controls with and without *FKBP5* rs1360780 genotype data in terms of gender (χ^2=0.108, p=0.773), age (t=-0.661(252), p=0.509), ethnicity (χ^2=13.33, p=0.261) and education (χ^2=2.604, p=0.640). The majority of cases (n=137, 59.3%) and controls (n=103, 53.9%) were males and the mean age at interview was 29.4 years for cases and 28.8 years for controls. Cases were more likely to be from a black or other minority group compared to controls (χ^2=32.842, p=0.001). No significant differences were found between the psychosis cases and community controls in terms of gender (χ^2=1.234, p=0.267), and age (t=-0.687(420), p=0.171).

Table 6.3 presents the distribution of the three *FKBP5* genotypes (*T/T*, *C/T*, *C/C*) along with the expected prevalence according to the HWE equation: [where *T* has a frequency of p and C has a frequency of (1-p), expected genotype frequencies are as follows: *T/T*= p^2, *C/T*= 2p(1-p) and *C/C*= $(1-p)^2$] and the findings of the HWE tests.

Table 6.3 Hardy-Weinberg Equilibrium results for *FKBP5* genotypes in cases and controls

Group	***T/T n***	***C/T N***	***C/C n***	***HWE X^2***	***Exact P***
Controls (N=191)				0.064	0.800
Observed	21	87	83		
Expected	21.78	85.44	83.78		
Cases (N=231)				1.257	0.262
Observed	36	100	95		
Expected	32.02	107.97	91.02		

HWE, Hardy-Weinberg Equilibrium.

The results of the HWE analysis indicate that both the controls (χ^2=0.064, *p*=0.800) and psychosis cases (χ^2=1.257, *p*=0.262) in this sample were in equilibrium with regards to this locus. The non-significant findings suggest that the *T* and *C* alleles were independently distributed in these samples and thus there was no genetic bias in selection of the sample nor were there any major genotyping errors. The distributions of the *FKBP5* genotypes were similar between psychosis cases and controls and this was confirmed by a non-significant result for Cuzick's non-parametric trend test (*z*=0.90, *p*=0.366). Therefore, there was no main effect of the *FKPB5* polymorphism on psychosis in this sample.

Association between genotype and childhood adversity in psychosis

COMT Val158Met

The proportion of participants with each genotype was compared for those with and without a history of childhood adversity. Cuzick's non-parametric trend test was conducted to investigate potential associations between genotype and adverse childhood experiences. The results are presented separately for cases and controls in Tables 6.4 and 6.5, respectively.

Table 6.4 Distribution of *COMT* genotypes by history of childhood adversity in cases

Type of adversity	***Val/Val***	***Val/Met***	***Met/Met***		
	n (%)	***n (%)***	***n (%)***	**Z**	***P***
Parental separation				1.20	0.229
Yes (n=142)	56 (39.4)	77 (54.2)	9 (6.3)		
No (n=107)	40 (37.4)	52 (48.6)	15 (14.0)		
Parental loss				-1.33	0.184
Yes (n=29)	8 (27.6)	17 (58.6)	4 (13.1)		
No (n=217)	86 (39.6)	111 (51.2)	20 (9.2)		
Total adversity				1.05	0.292
2 or more (n=74)	30 (40.5)	37 (50.0)	7 (9.5)		
1 (n=109)	42 (38.5)	61 (56.0)	6 (5.5)		
0 (n=67)	24 (35.8)	32 (47.8)	11 (16.4)		

Met, methionine. *Val*, valine.

For psychosis cases, there was no evidence of a significant correlation between *COMT* genotype and parental separation (p=0.229), parental loss (p=0.184) and single or multiple adverse experiences (p=0.292).

Table 6.5 Distribution of *COMT* genotypes by history of childhood adversity in controls

Type of adversity	***Val/Val***	***Val/Met***	***Met/Met***		
	n (%)	***n (%)***	***n (%)***	**Z**	***P***
Parental separation				0.77	0.441
Yes (n=68)	27 (39.7)	35 (51.5)	6 (8.8)		
No (n=132)	47 (35.6)	69 (52.3)	16 (12.1)		

Type of adversity	*Val/Val* *n (%)*	*Val/Met* *n (%)*	*Met/Met* *n (%)*	Z	*P*
Parental loss				0.55	0.583
Yes (n=11)	5 (45.5)	5 (45.5)	1 (9.1)		
No (n=189)	69 (36.5)	99 (52.4)	21 (11.1)		
Total adversity				1.07	0.283
2 or more (n=35)	14 (40.0)	20 (57.1)	1 (2.9)		
1 (n=62)	23 (37.1)	32 (51.6)	7 (11.3)		
0 (n=104)	37 (35.6)	53 (51.0)	14 (13.4)		

Met, methionine. *Val*, valine.

Amongst controls there was no evidence of a significant effect of genotype for parental separation (p=0.441), parental loss (p=0.583) and total number of adverse experiences (p=0.283). Therefore, no significant gene-environment correlations were found overall between the *COMT Val158Met* genotype and childhood adversity.

AKT1 rs2494732

The results of Cuzick's non-parametric trend test to investigate the potential associations between *AKT1* rs2494732 genotype and adverse childhood experiences are presented separately for cases and controls in Tables 6.6 and 6.7, respectively.

Table 6.6 Distribution of *AKT1* genotypes by history of childhood adversity in cases

Type of adversity	*C/C* *n (%)*	*C/T* *n (%)*	*T/T* *n (%)*	Z	*P*
Parental separation				-1.39	0.163
Yes (n=139)	26 (18.7)	75 (54.0)	38 (27.3)		
No (n=105)	28 (26.7)	53 (50.4)	24 (22.9)		

Type of adversity	*C/C* *n (%)*	*C/T* *n (%)*	*T/T* *n (%)*	Z	*P*
Parental loss				-0.30	0.767
Yes (n=29)	5 (17.2)	17 (58.7)	7 (24.1)		
No (n=212)	49 (23.1)	108 (50.9)	55 (26.0)		
Total adversity				-0.96	0.338
2 or more (n=73)	14 (19.2)	37 (50.7)	14 (30.1)		
1 (n=108)	24 (22.2)	59 (54.6)	25 (23.2)		
0 (n=64)	16 (25.0)	32 (50.0)	16 (25.0)		

For psychosis cases, there was no evidence of association between *AKT1* genotypes and parental separation (p=0.163) and loss (p=0.767), as well as for total number of adversities (p=0.338).

Table 6.7 Distribution of *AKT1* genotypes by history of childhood adversity in controls

Type of adversity	*C/C* *n (%)*	*C/T* *n (%)*	*T/T* *n (%)*	Z	*P*
Parental separation				1.25	0.211
Yes (n=67)	19 (28.4)	31 (46.2)	17 (25.4)		
No (n=123)	24 (19.5)	62 (50.4)	37 (30.1)		
Parental loss				1.15	0.251
Yes (n=11)	4 (36.4)	5 (45.5)	2 (18.1)		
No (n=179)	39 (21.8)	88 (49.2)	52 (29.0)		
Total adversity				1.50	0.134
2 or more (n=34)	11 (32.4)	14 (44.1)	8 (23.5)		
1 (n=61)	14 (23.0)	31 (50.8)	16 (26.2)		
0 (n=96)	18 (18.7)	48 (50.0)	30 (31.3)		

Amongst controls, there was no evidence of a significant effect of genotype for parental separation (p=0.211), parental loss (p=0.251) and total number of adversities (p=0.134). Therefore, no correlations were found between the *AKT1* genotype and childhood adversity amongst cases or controls.

FKBP5 rs1360780

The results of Cuzick's non-parametric trend test to investigate potential associations between *FKBP5* rs1360780 genotype and adverse childhood experiences are presented for cases and controls in Tables 6.8 and 6.9, respectively.

Table 6.8 Distribution of *FKBP5* rs1360780 genotypes by history of childhood adversity in cases

Type of adversity	***T/T*** ***n (%)***	***C/T*** ***n (%)***	***C/C*** ***n (%)***	**z**	***P***
Parental separation				-0.31	0.760
Yes (n=134)	24 (17.9)	50 (37.3)	60 (44.8)		
No (n=96)	12 (12.5)	49 (51.0)	35 (36.5)		
Parental loss				-0.97	0.332
Yes (n=29)	4 (13.8)	10 (34.5)	15 (51.7)		
No (n=198)	31 (15.7)	88 (44.4)	79 (39.9)		
Total adversity				-1.92	0.104
2 or more (n=72)	9 (12.5)	30 (41.7)	33 (45.8)		
1 (n=102)	17 (16.7)	40 (39.2)	45 (44.1)		
0 (n=57)	10 (17.5)	30 (52.6)	17 (29.8)		

For psychosis cases, there was no evidence of a significant effect of genotype for separation from parents (p=0.760), loss of parents (p=0.332) and total number of adversities (p=0.104).

Table 6.9 Distribution of *FKBP5* genotypes by history of childhood adversity in controls

Type of adversity	***T/T*** ***n (%)***	***C/T*** ***n (%)***	***C/C*** ***n (%)***	**z**	***P***
Parental separation				1.42	0.156
Yes (n=66)	10 (15.2)	31 (47.0)	25 (37.9)		
No (n=124)	11 (8.9)	56 (45.2)	57 (46.0)		
Parental loss				-1.15	0.248
Yes (n=11)	1 (9.1)	3 (27.3)	7 (63.6)		
No (n=179)	20 (11.2)	84 (49.6)	75 (41.9)		
Total adversity				0.89	0.373
2 or more (n=34)	5 (14.7)	12 (35.3)	17 (50.0)		
1 (n=61)	10 (16.4)	28 (45.9)	23 (37.7)		
0 (n=96)	6 (6.2)	47 (49.0)	43 (44.8)		

Amongst controls there was no evidence of a significant effect of genotype for parental separation (p=0.156), parental loss (p=0.248) and total number of adversities (p=0.373) with *FKBP5* rs1360780 genotype. Therefore, overall, no significant correlations were found between the *FKBP5* genotype and childhood adversity.

Empirical analyses on oligogenic-score x childhood adversity interaction on risk of psychotic disorders

Table 6.10 shows the results of the regression analyses of the oligogenic risk score x childhood adversity interaction in the onset of psychosis.

Table 6.10 Main effect of different forms of childhood adversity and their interactions with 'oligogenic risk score' on the presence of psychotic disorder

Type of childhood adversity	Unadjusted RD	95% CI	*P* value	Adjusted RD*	95% CI	*P* value
Parental separation						
Low oligogenic risk (n=145)	**1.08**	0.37-1.79	**0.003**	**1.10**	0.31-1.91	**0.007**
Medium oligogenic risk (n=143)	**0.87**	0.13-1.62	**0.021**	0.38	-0.54-1.30	0.420
High oligogenic risk (n=122)	0.39	-0.34-1.13	0.294	0.32	-0.46-1.11	0.415
GxE interaction	-0.08	-0.20-0.04	0.179	-0.12	-0.23;-0.02	0.018
Parental loss						
Low oligogenic risk (n=145)	0.84	-0.26-1.95	0.135	0.48	-0.84-1.79	0.478
Medium oligogenic risk (n=142)	1.02	-0.37-2.40	0.150	0.85	-0.63-2.33	0.260
High oligogenic risk (n=120)	0.60	-0.83-1.98	0.419	0.57	-0.88-2.08	0.444
GxE interaction	-0.03	-0.21-0.16	0.781	-	-	-
Total adversity						
Low oligogenic risk (n=147)	**0.68**	0.24-1.12	**0.002**	**0.57**	0.08-1.07	**0.023**
Medium oligogenic risk (n=143)	**0.94**	0.44-1.44	**<0.001**	**0.66**	0.10-1.22	**0.020**
High oligogenic risk (n=122)	0.19	-0.32-0.69	0.469	0.06	-0.48-0.60	0.834
GxE interaction	-0.04	-0.12-0.03	0.231	-0.07	-0.13;-0.01	0.028

*Adjusted for gender, education level and age at interview. CI, confidence interval. GxE, genetic by environmental interaction. RD, risk difference. – indicates unable to calculate values due to at least one cell containing a zero value.

Results of this preliminary GxE investigation show that, in individuals with low and medium oligogenic risk, reports of parental separation and total number of childhood adversities are associated with psychosis caseness. Adjusting for demographic confounders, the association between parental separation and psychosis in participants with medium oligogenic risk fell short of statistical significance. No association was found between reports of parental loss and psychosis stratifying for oligogenic risk. Furthermore, no significant additive interactions were found overall between childhood adversity and oligogenic risk for presence of psychotic disorder.

However, given the significant association between parental separation and total adversities in carriers of low (up to two risk alleles) and medium (three risk alleles) oligogenic risk, I hypothesized that the association with psychosis could be driven by the effect of single candidate genes. Therefore, I subsequently explored the interplay between these two measures of childhood adversities with each of the selected candidate genes in the onset of psychosis.

COMT by childhood adversity interaction in psychosis

Firstly, the potentially moderating effect of the *COMT Val158Met* polymorphism on the association between reported history of any adverse experience before 17 years of age and psychotic disorder was explored. As it was predicted that the *Val* allele was most likely to interact with childhood adversity, the analysis was conducted stratified by genotypes (*Val/Val*, *Val/Met*, *Met/Met*). Table 6.11 presents the main effects of each form of adversity and their interactions with *COMT* on the presence of psychosis.

Table 6.11 Main effect of different forms of childhood adversity and their interactions with each *COMT Val158Met* genetic model on the presence of psychotic disorder

Type of childhood adversity	Cases *n* (%)	Controls *n* (%)	Unadjusted RD	95% CI	*P* value	Adjusted RD*	95% CI	*P* value
Parental separation								
Absent	107 (43.0)	132 (66.0)						
Present	142 (57.0)	68 (34.0)						
Overall (n=439)			**0.20**	**0.11-0.30**	**<0.001**	**0.20**	**0.11-0.3**	**<0.001**
Met/Met genotype (n=46)			0.06	-0.19-0.32	0.625	0.00	-0.01-0.01	0.702
Val/Met genotype (n=227)			**0.24**	**0.11-0.37**	**<0.001**	**0.25**	**0.12-0.38**	**<0.001**
Val/Val genotype (n=166)			**0.20**	**0.04-0.35**	**0.012**	**0.19**	**0.04-0.35**	**0.014**
GxE interaction			-0.01	-0.14-0.14	0.994	0.01	-0.15-0.13	0.911
Total adversity								
0	67 (26.8)	104 (51.7)						
1	109 (43.6)	62 (30.8)						
2 or more	74 (29.6)	35 (17.5)						
Overall (n=451)			**0.14**	0.08-0.19	**<0.001**	**0.09**	0.03-0.15	**0.003**
Met/Met genotype (n=46)			**0.10**	0.00-0.19	**0.043**	-0.01	-0.19-0.17	0.900
Val/Met genotype (n=235)			**0.14**	0.06-0.22	**<0.001**	**0.09**	0.01-0.17	**0.029**
Val/Val genotype (n=170)			**0.13**	0.04-0.23	**0.006**	0.09	-0.00-0.19	0.056
GxE interaction			-0.02	-0.11-0.06	0.614	-0.03	-0.09-0.04	0.390

*Adjusted for gender, education level and age at interview. CI, confidence interval. GxE, genetic by environmental interaction. RD, risk difference.

Overall, childhood adversity was significantly associated with the presence of psychosis even after adjustment for confounders. Specifically, a significant association with psychosis was found for parental separation (p<0.001) and the total number of adversities (p<0.001). Individuals with one or two copies of the *Val* allele and reporting a history of parental separation were more likely to have a psychotic disorder in this sample. The total number of adversities was associated with psychosis regardless of *COMT* genotype (all p<0.05), though after adjusting for demographic confounders the association remained significant only in the *Val/Met* carriers. No significant interactions with childhood adversity were found under an additive *COMT* genetic model.

AKT1 by childhood adversity interaction in psychosis

Table 6.12 presents the main effects of each form of adversity and their interactions with *AKT1* rs249432 on the presence of psychosis. Overall, the significant association with psychosis was maintained for parental separation (p<0.001) and total number of adversities (p<0.001). Individuals with one copy of the *C* allele and a reported history of parental separation or multiple adversities had increased odds of psychotic disorder. No significant interactions were found for parental separation or for the total number childhood adversities.

Table 6.12 Main effect of different forms of childhood adversity and their interactions with each *AKT1* rs2494732 genetic model on the presence of psychotic disorder

Type of childhood adversity	Cases *n* (%)	Controls *n* (%)	Unadjusted RD	95% CI	*P* value	Adjusted RD*	95% CI	*P* value
Parental separation								
Absent	105 (43.0)	123 (64.7)						
Present	139 (57.0)	67 (35.3)						
Overall (n=424)			**0.19**	**0.09-0.28**	**<0.001**	**0.19**	**0.09-0.28**	**<0.001**
TT genotype (n=113)			**0.27**	**0.08-0.46**	**0.005**	**0.27**	**0.08-0.45**	**0.005**
CT genotype (n=215)			**0.24**	**0.11-0.37**	**<0.001**	**0.24**	**0.11-0.37**	**<0.001**
CC genotype (n=96)			0.00	0.21-0.20	0.965	0.02	0.18-0.22	0.820
GxE interaction			-0.11	-0.24-0.02	0.107	0.11	-0.24-0.02	0.109
Total adversity								
0	64 (26.1)	96 (50.3)						
1	108 (44.1)	61 (31.9)						
2 or more	73 (29.8)	34 (17.8)						
Overall (n=436)			**0.13**	0.07-0.19	**<0.001**	**0.14**	0.08-0.19	**<0.001**
TT genotype (n=117)			**0.18**	0.07-0.29	**0.001**	**0.18**	0.07-0.29	**0.002**
CT genotype (n=222)			**0.15**	0.08-0.24	**<0.001**	**0.16**	0.08-0.24	**<0.001**
CC genotype (n=97)			0.03	-0.10-0.16	0.615	0.05	-0.07-0.18	0.400
GxE interaction			-0.05	-0.13-0.02	0.181	-0.05	-0.13-0.03	0.187

*Adjusted for gender, level of education and age at interview. CI, confidence interval. GxE, genetic by environmental interaction. RD, risk difference.

FKBP5 by childhood adversity interaction in psychosis

Finally, the main effects of each form of childhood adversity and their interactions with *FKBP5* on the presence of psychosis are presented in Table 6.13. Overall, also in this sample both measures of adversity remained significantly associated with greater risk of psychosis even after adjustment for confounders. Specifically, a significant association with psychosis was found for parental separation (p<0.001) and total number of adversities (p<0.001). Individuals with no copies of the risk allele (*C/C*) and reported history of parental separation were more likely to have a psychotic disorder. Patients with no copy (C/C) or one copy of the risk allele *(C/T)* reported a higher number of adversities. No significant interactions were demonstrated for these forms of adversity.

Table 6.13 Main effect of different forms of childhood adversity and their interactions with each *FKBP5 rs1360780* genetic model on the presence of psychotic disorder

Type of childhood adversity	Cases *n* (%)	Controls *n* (%)	Unadjusted RD	95% CI	*P* value	Adjusted RD*	95% CI	*P* value
Parental separation								
Absent	96 (41.7)	124 (65.3)						
Present	134 (58.3)	66 (34.7)						
Overall (n=412)			**0.21**	**0.11-0.30**	**<0.001**	**0.20**	**0.11-0.30**	**<0.001**
CC genotype (n=173)			**0.30**	**0.16-0.45**	**<0.001**	**0.30**	**0.15-0.45**	**<0.001**
CT genotype (n=182)			0.12	-0.03-0.27	0.109	0.13	-0.02-0.28	0.092
TT genotype (n=57)			0.14	-0.12-0.40	0.297	0.14	-0.13-0.41	0.309
GxE interaction			-0.09	-0.23-0.04	0.172	-0.09	-0.23-0.04	0.168
Total adversity								
0	57 (24.7)	96 (50.3)						
1	102 (44.1)	61 (31.9)						
2 or more	72 (31.2)	34 (17.8)						
Overall (n=422)			**0.14**	0.08-0.20	**<0.001**	**0.09**	0.03-0.16	**0.003**
CC genotype (n=178)			**0.18**	0.09-0.26	**<0.001**	**0.13**	0.03-0.22	**0.008**
CT genotype (n=187)			**0.16**	0.07-0.25	**0.001**	**0.10**	0.01-0.19	**0.021**
TT genotype (n=57)			-0.02	-0.19-0.15	0.806	-0.08	-0.25-0.10	0.403
GxE interaction			-0.07	0.15-0.02	0.129	-0.07	-0.15-0.01	0.103

*Adjusted for gender, level of education, and age at interview. CI, confidence interval. GxE, genetic by environmental interaction. RD, risk difference.

Discussion

No main effect of the selected polymorphisms was found on psychosis case status or childhood adversity in this sample. Previous findings on *COMT Val158Met* have been inconsistent (Glatt et al., 2003) and even a large family-based study found only modest associations between this variant and schizophrenia (Chen et al., 2004b). Moreover, recent meta-analyses concluded there was no, or at best only weak, evidence of *COMT* genotype increasing risk for psychosis (Fan et al., 2005; Munafo et al., 2005; Ripke et al., 2013). My findings on *AKT1* rs2494732 polymorphism and psychotic disorder in this sample are in contrast with some previous studies that found an association between this candidate gene and schizophrenia (Bolog et al., 2012; Karege et al., 2012; Norton et al., 2007; Thiselton et al., 2008). However, the absence of a main effect of *FKBP5* rs1360780 on psychosis is in line with Gawlik et al. (2006) that found no association of rs1360780 with affective psychosis.

There was, as expected and shown previously in this thesis, a main effect of adverse childhood experiences on presence of psychotic disorder. This association was evident in carriers of at least one *COMT Val* allele for parental separation and multiple childhood adversities. This is consistent with previous studies that have shown the greatest impact of stressful events on psychotic symptoms amongst individuals with at least one *Val* allele compared to those homozygous for the *Met* allele (Simons et al., 2009; Stefanis et al., 2007) but not with other studies that have found greater sensitivity for the *Met/Met* genotype (Myin-Germeys et al., 2006; van Winkel et al., 2008a). This discrepancy could be partly due to differences in the demographics of the samples, type of psychotic outcome and intensity of the stressors studied (Simons et al., 2009; van Winkel et al., 2008b). The main effect of childhood adversity on psychosis onset was confirmed for *AKT1* and *FKBP5*, with carriers of no copies or one copy of the risk allele being significant more likely to be a psychosis case if they also reported parental separation and multiple adversities in childhood. This is in line with a previous study that found an association between *FKBP5* rs1360780 and

psychosis only after adjusting for cannabis use and parental separation in the analysis (Ajnakina et al., 2014).

There was no evidence of genotype by childhood adversity interaction for presence of psychotic disorder. These results are in line with a previous study which found no interaction between COMT genotype and childhood maltreatment in predicting schizophreniform disorder at 26 years of age (Caspi et al., 2005). However, previous animal studies have shown an interaction between *COMT* and maternal care in mice (Zhang et al., 2005). A three-way interaction between the COMT genotype *Val* alleles, childhood maltreatment, and adolescent cannabis use has also been reported in the etiology of psychotic experiences (Alemany et al., 2014; Vinkers et al., 2013). Therefore, it might be that the lack of an interaction effect between *COMT* and childhood adversity on psychosis in the current sample could be due to other environmental factors having affected psychosis case status. Similarly, previous studies found an interaction between *AKT1* rs2494732 also with cannabis use in first-episode psychosis (Di Forti et al., 2012; van Winkel et al., 2011b).

Consistent with Collip et al. (2013) study, I did not find a significant interaction between *FKBP5 rs1360780* SNP and childhood adversity in psychotic disorder. However, this SNP was previously found to interact with trauma in other studies examining adult PTSD symptoms (Binder et al., 2008), peri-traumatic dissociation in children after medical trauma (Koenen & Uddin, 2010) and depression (Zimmerman et al., 2011).

In conclusion, the current study failed to provide evidence of an interaction between specific candidate genes and childhood adversity in psychosis onset and, therefore, in this particular sample the specific genotypes investigated did not seem to moderate the effect of childhood adversity on presence of a psychotic disorder.

Results section 6.2

Genotype, childhood adversity and one-year outcomes

COMT Val158Met

The potentially moderating effect of the *COMT Val158Met* polymorphism on the association between reported history of adverse experiences in childhood and one year psychosis outcomes was also tested. Given that parental separation was associated with psychosis onset in *Val* carriers (in the previous section) and independently associated with length of hospital admission and compliance with medication at one year (as shown in Chapter 4), the moderating effect of the *COMT Val158Met* polymorphism on these outcomes was investigated.

COMT Val158Met did not show a significant association with psychosis outcomes, namely length of hospital admission (Adj RD=0.09, 95% CI: -0.06-0.24, *p*=0.257) and compliance with medication at 12 months (Adj RD=0.0, 95% CI: -0.06-0.21, *p*=0.297). Table 6.14 presents the main effects of parental separation, stratified by genotypes (*Val/Val*, *Val/Met*, *Met/Met*), and its interaction with *COMT* on psychosis outcomes. The main effect of parental separation on compliance with medications at one year from illness onset reported in Chapter 4 (Results section 4.2) was confirmed in this subsample of cases with *COMT Val158Met* polymorphism data available (n=179). Individuals with two copies of the *Val* allele and reporting a history of parental separation were significantly more likely to be non-compliant with medication one year after psychosis onset (*p*=0.013). The association increased after adjusting for duration of untreated psychosis (DUP) and compliance with medications at baseline (RD=0.38, *p*=0.002): the absolute risk of being non-compliant with medication at one year was 30% less in cases reporting no separation from parents during childhood for at least six months compared to those reporting parental separation. However, no significant interactions were found between parental separation and *COMT* genetic models on medication compliance at one year.

Table 6.14 Main effect of parental separation and its interaction with each *COMT Val158Met* genetic model on one-year outcomes of psychosis

Follow-up outcome			RD	95% CI	*P* value	Adjusted RD*	95% CI	*P* value
Compliance with medication	***Compliant n (%)***	***Not compliant n(%)***						
Parental separation								
Absent	57 (49.1)	21 (33.3)						
Present	59 (50.9)	42 (66.7)						
Overall (n=179)			**0.16**	0.01-0.31	**0.031**	**0.30**	0.13-0.47	**0.001**
Met/Met genotype (n=21)			-0.11	-0.29-0.08	0.263	0.35	-0.40-1.09	0.361
Val/Met genotype (n=90)			0.16	-0.03-0.36	0.105	**0.26**	0.08-0.45	**<0.001**
Val/Val genotype (n=68)			**0.28**	0.06-0.50	**0.013**	**0.38**	0.14-0.61	**0.002**
GxE interaction			0.09	-0.12-0.30	0.397	0.03	-0.21-0.27	0.796
Hospital admission days	***Less than 49 days n (%)***	***49 days or more n (%)***						
Parental separation								
Absent	52 (49.1)	34 (34.3)						
Present	54 (50.9)	65 (65.7)						
Overall (n=205)			**0.14**	0.01-0.29	**0.049**	0.22	-0.00-0.44	0.056
Met/Met genotype (n=22)			0.34	-0.08-0.78	0.116	**0.97**	0.97-0.97	**<0.001**
Val/Met genotype (n=103)			0.13	-0.08-0.33	0.232	0.32	-0.2-0.66	0.062
Val/Val genotype (n=80)			0.11	0.11-0.34	0.324	-0.09	-0.45-0.27	0.624
GxE interactions			0.00	-0.21-0.21	0.998	-0.47	-0.60-0.32	<0.001

*Adjusted for DUP and baseline compliance with medications (for compliance with medications at 12 months), DUP and baseline GAF symptoms scale (for hospital admission days). CI, confidence interval. RD, risk difference. DUP, duration of untreated psychosis, GAF, Global Assessment of Functioning.

The main effect of parental separation on days of hospital admission over the first year since presentation for psychosis was maintained in this subsample of cases with *COMT Val158Met* and follow-up data (p=0.049). However, no significant differences in this association were found stratifying by *COMT* genotypes. After adjusting for DUP and baseline overall clinical functioning measured by the GAF-symptoms scale, individuals with no copies of the *Val* allele and reporting a history of parental separation were significantly more likely to have a longer hospital stay (p<0.001) compared to those cases with no reported history of parental separation. These results were confirmed by the interaction analyses, with negative values indicating a significant effect of parental separation on the length of hospital admission in the absence of *COMT Val158Met* genetic risk.

AKT1 rs2494732

Next, the potentially moderating effect of the *AKT1* rs2494732 polymorphism on the association between reported history of childhood adverse experiences and one year psychosis outcomes was explored. Similarly to *COMT* Val158Met, parental separation was associated with psychosis onset in carriers of the risk (*C*) allele; therefore, the moderating effect of the *AKT1* rs2494732 polymorphism on length of hospital stay and compliance with medications was investigated. There was no association between *AKT1* rs2494732 with length of hospital admission over the first year of illness (Adj RD=-0.04, 95% CI: -0.14-0.06, p=0.415) and compliance with medication at 12 months (Adj RD=-0.03, 95% CI: -0.15-0.09, p=600).

Table 6.15 presents the main effects of parental separation, stratified by genotypes (*T/T*, *C/T*, *C/C*), and its interaction with *AKT1* on psychosis outcomes. The main effect of parental separation on compliance with medications at one year from illness onset was confirmed in this subsample of cases with *AKT1* rs2494732 polymorphism data available (n=176). Individuals with one copy of

the risk allele ('*C*') and reporting a history of parental separation were significantly more likely to be non-compliant with medication one year after psychosis onset (p=0.043). However, after adjusting for DUP and compliance with medications at baseline the association fell short of statistical significance (p=0.068). In the adjusted model, individuals with no copies (p=0.018) or two copies (p=0.039) of the *C* allele and reporting a history of parental separation were significantly more likely to be non-compliant with medication one year after psychosis presentation than those without these risk factors. Therefore, no significant interactions were found between parental separation and *AKT1* genetic models in relation to compliance with medications at one-year.

Table 6.15 Main effect of parental separation and its interaction with each *AKT1* rs2494732 genetic model on the one year first episode psychosis outcomes

Follow-up outcome			**RD**	**95% CI**	***P* value**	**Adjusted RD***	**95% CI**	***P* value**
Compliance with medication	***Compliant n (%)***	***Not compliant n (%)***						
Parental separation								
Absent	56 (49.1)	21 (33.9)						
Present	58 (50.9)	41 (66.1)						
Overall (n=176)			**0.16**	0.01-0.30	**0.040**	**0.31**	0.15-0.48	**<0.001**
TT genotype (n=48)			0.17	-0.01-0.36	0.066	**0.33**	0.06-0.60	**0.018**
CT genotype (n=91)			**0.20**	0.01-0.40	**0.043**	0.27	-0.02-0.55	0.068
CC genotype (n=37)			0.09	-0.31-0.48	0.660	**0.27**	0.01-0.54	**0.039**
GxE interaction			0.05	-0.16-0.25	0.648	-0.03	-0.26-0.19	0.775
Hospital admission days	***Less than 49 days n (%)***	***49 days or more n (%)***						
Parental separation								
Absent	52 (50.5)	34 (34.3)						
Present	51 (49.5)	65 (65.7)						
Overall (N=202)			**0.15**	0.01-0.30	**0.038**	0.22	-0.01-0.44	0.055
TT genotype (n=54)			0.19	-0.09-0.46	0.193	-0.03	-0.34-0.28	0.853
CT genotype (n=105)			0.14	-0.06-0.34	0.158	0.12	-0.23-0.48	0.507
CC genotype (n=43)			0.18	-0.15-0.51	0.279	**0.65**	0.31-1.00	**<0.001**

Follow-up outcome	RD	95% CI	*P* value	Adjusted RD*	95% CI	*P* value
GxE interactions						
Additive model x PS	-0.04	-0.24-0.15	0.665	**0.28**	0.03-0.54	**0.029**
Recessive model x PS	-0.11	-0.44-0.23	0.530	0.41	-0.01-0.83	0.054
Dominant model x PS	-0.02	-0.34-0.29	0.885	0.25	-0.21-0.72	0.287

*Adjusted for DUP and baseline compliance with medications (for compliance with medications at 12 months), DUP and baseline GAF symptoms scale (for hospital admission days). CI, confidence interval. RD, risk difference. DUP, duration of untreated psychosis, GAF, Global Assessment of Functioning.

The main effect of parental separation on length of hospital admission over the first year of psychosis was also confirmed in those cases with *AKT1* rs2494732 data available (p=0.038). Trends in difference in risks were found stratifying for *AKT1* genotypes in those cases with none or one risk allele. After adjusting for DUP and baseline overall clinical functioning measured by GAF, the main effect of parental separation in the overall sample fell short of statistical significance (p=0.055) but, surprisingly, became stronger in those individuals with two copies of the *C* allele, with 65% of reduction of absolute risk of longer hospital stay in those cases reporting no history of parental separation compared to those who did report such adversity (p<0.001). Consequently, a significant interaction between parental separation and *AKT1* additive model on hospital admission days was found (p=0.029), though this could be considered as a chance finding and it fell short of statistical significance when a Bonferroni correction for multiple testing was applied (p=0.05/6=0.008).

FKBP5 rs1360780

Given that parental separation did not show a significant association with psychosis onset on carriers of *FKBP5* rs1360780 risk allele '*T*', the potentially moderating effect of this polymorphism on the association between reported history of childhood parental separation and one year psychosis outcomes was not explored.

Discussion

The main effect of parental separation on psychosis outcomes was confirmed also in this subsample of cases with data available on selected genotypes. Specifically parental separation in childhood was associated with both hospital admission days over the first year of illness and with compliance with medication at 12 months.

This sample of individuals with first episode psychosis followed-up over one year from illness onset failed to provide evidence of an interaction between *COMT Val158Met* and parental separation on compliance with medication and length of hospital admission of psychosis cases at one year follow-up. These results are in line with previous studies, investigating the effect of *COMT Val158Met* on outcomes of psychiatric disorders. Specifically, Andersson et al. (2013) found no effect of the *COMT Val158Met* polymorphism on response cognitive behavior therapy (CBT) for social anxiety disorder 12 months after treatment. In line with these findings, other studies on treatment response in schizophrenia found no interaction between *COMT Val158Met* and antipsychotic drugs on schizophrenia symptoms at three months (Tybura et al., 2012) and between *COMT Val158Met* and cognitive remediation therapy on cognitive outcomes (Greenwood et al., 2011). The *COMT Val158Met* genotype has been reported to be related to the severity of positive and negative symptoms rather than to clinical response in general population and first episode psychosis studies. Stefanis et al. (2007) reported that carriers of the *Val* allele had a greater increase in psychotic symptoms over an 18-month period following exposure to a stressful situation than participants homozygous for the *Met* allele. *Val* homozygote patients showed higher positive symptoms at 6 months and higher negative symptoms than *Met* homozygote patients and 6 weeks respectively (Molero et al., 2007; Pelayo-Terán et al., 2011). However, in the current study I found no significant differences between cases reporting parental separation and those without such adversity in terms of number of days at hospital over one

year from illness onset, which could be considered as a proxy measure of the patient's severity of illness.

Evidence of interaction was found between history of parental separation for at least six months and *AKT1* genotype on days of hospital admission in this psychosis sample over the first year of illness, under an additive genetic model. However, this interaction was not confirmed by the dominant and recessive genetic models and did not stand correction for multiple testing. Despite previous studies highlighting the association between *AKT1* and sub-clinical and clinical psychotic symptoms (Bruenig et al., 2014; Egan et al., 2001; Karege et al., 2012) as well as with mood disorders (Emamian et al., 2004), the effect of such specific genetic predisposition on the course of psychosis has not been investigated. *AKT1* has been reported to be associated with suicide attempts in patients with bipolar disorder (Magno et al., 2010) and, investigating the *AKT1* interplay with environmental risk factors, van Winkel et al. (2011b) found that genetic variation in *AKT1* may mediate both short-term as well as longer-term effects on psychosis expression associated with use of cannabis. Therefore, these findings on *AKT1* x childhood adversity interaction in psychosis outcomes are novel and require replication.

Methodological considerations

Although the present results may have some biological plausibility, it is important to cautiously consider them in light of several limitations. The most important consideration in this regard is low a priori probability of interaction and/or low statistical power (Duncan & Keller, 2011) issues that are more common in candidate gene approaches (Burton et al., 2009). Several studies (Boks et al., 2007; Garcia-Closas & Lubin, 1999; Hwang et al., 1994; Smith & Day, 1984), investigating the statistical power of G×E studies, have concluded that power to detect G×E interactions is even lower than power to detect genetic or

environmental main effects (Uher, 2014) and this was the case in the present study.

Nevertheless, the sample size was similar to, and in some cases exceeded, the number of participants utilised in previous studies. For example, Stefanis et al. (2007) included 306 army recruits whilst King et al. (2006) reported on just 80 psychosis patients, Henquet et al. (2006) on only 74 individuals and van Winkel et al. (2008a) on a mere 56 participants. It is estimated that 340 patients and 340 controls would be required to obtain 80% power for detection of GxE interaction, with a minor allele frequency of 0.5 and a significance level of 0.050.

Furthermore, this study may have failed to detect an interaction also because of the utilisation of self-report measures (e.g. CECA-Q; Bifulco et al., 2005), or because other environmental factors are driving the effect (eg, substance use [Di Forti et al., 2012] or stressful life events occurring in adulthood [Beards et al., 2013] as discussed in Chapter 4).

Moreover, this sample is multiethnic. This may be important in the light of the differences in allele frequency across the main ethnic groups (black and white Caucasian; Knowler et al., 1988). However, to account for the possibility of population stratification, all analyses were controlled for the potential confounding effect of ethnicity to reduce this potential bias in the results. In this sample, one (out of three) SNPs was also in Hardy–Weinberg disequilibrium. As SNPs in Hardy–Weinberg disequilibrium are less powerful, and do not tend to increase false-positive results (Fardo et al., 2009), the reported results are unlikely to be caused by Hardy–Weinberg disequilibrium, especially given the absence of quality control issues (the genotypes were successfully identified at rates (call rates) of between 79% and 85%).

Another limitation of this study is the possible effects of medication which were not controlled for in this study owing to limited detail of medication dosage collected at the time of testing and over the follow-up period. These medications could have interacted with genotype to affect the clinical and

social/vocational functioning of clinical cases (Wang et al., 2010). In order to reduce the effect of premorbid adjustment I included DUP and other measures of clinical and social functioning in the adjusted model.

The main strength of this study is its design. A case-control strategy is the gold standard design to test GxE interaction hypotheses (Khoury & Flanders, 1996). In keeping with good methodological practice for a GxE replication study (Moffitt et al., 2005), only the candidate genetic variant were genotyped, according to the a priori hypothesis suggested by the literature I set to replicate. However, the final sample size was underpowered to estimate whether *COMT*, *AKT1* and *FKBP5* risk allele carriers with exposure to childhood adversity had a significantly increased risk of psychotic disorders and worse outcomes over the first year of illness compared to subjects with neither of these risk factors. Therefore, these findings do not provide definite evidence against a possible role of *COMT*, *AKT1* and *FKBP5* genotypes in modifying the effect of childhood adversity on risk of psychotic disorders and on its course.

Synthesis of Chapter 6

In conclusion, the results of this study confirm the main effect of childhood adversity on psychosis onset and selected one-year outcomes. Individuals with one or two copies of the *COMT* and *AKT1* risk alleles reporting either history of parental separation or multiple adversities were more likely to be psychosis patients than controls. In contrast, childhood adversity was associated with psychosis onset in the absence of the *FKBP5* risk allele. There was no evidence of candidate genotypes by childhood adversity interactions in relation to psychosis onset. In terms of outcomes, *COMT* Met/Met carriers had longer psychiatric hospital stays compared to those *Val* allele carriers. Furthermore, *AKT1* interacted with parental separation in increasing the length of hospital admission over the first year.

However, these findings should be treated as extremely tentative given the small number of participants obtained via convenience methods and the ethnic diversity of the sample. It is likely that many alleles or genes of relatively small effect may collectively affect the risk of exposure to or the vulnerability to the effects of childhood adversity. As discussed in Chapter 2, findings from the GWAS of both bipolar disorder and schizophrenia indicated a polygenic model as underlying the genetics of psychotic disorders (Psychiatric Genomic Consortium, 2014). Such data suggests that polygenic scores might have to replace single gene variants in studies testing GxE interaction hypothesis. The summed effect of several genes of small effect may affect individual susceptibility to known environmental risk factors, such as childhood adversity, significantly increasing the likelihood of psychotic disorders and impacting on the course of illness. In the next, and final, chapter, I therefore present findings from a pilot investigation using a measure of 'polygenic' risk to simultaneous analyze several alleles or genes in the context of gene-environment correlation and interaction in the onset of psychosis.

CHAPTER 7 - Pilot study of the interplay between polygenic risk scores and childhood adversity on presence of psychotic disorder

Aims of this chapter

This pilot study focused on polygenic information to test for GxE interaction in first-episode psychosis, and examined whether polygenic risk scores interact with history of childhood trauma in a subsample of the GAP study.

I aimed to:

1. Establish the association of polygenic risk scores, childhood adversity and psychosis case status in this GAP subsample;
2. Test for a correlation between polygenic risk score and exposure to childhood adversity in psychosis cases and controls;
3. Explore a polygenic risk score by childhood adversity interaction for presence of psychotic disorder.

Results

Sample characteristics

Data on childhood adversity and polygenic risk score were available from a total of 86 White first-episode psychosis cases and 110 White controls drawn from the GAP study. Table 7.1 describes the characteristics of the subsample used for this pilot analysis.

Table 7.1 Subsample characteristics for this polygenic pilot analysis

	Cases (*N*=86) *n* (%)	**Controls (*N*=110) *n* (%)**	**Chi-square**	**df**	**p value**
Demographic variable					
Gender			0.18	1	0.773
Men	48 (55.8)	58 (52.7)			
Women	38 (44.2)	52 (47.3)			
Level of education			**26.27**	4	**<0.001**
No qualification	20 (23.5)	2 (2.0)			
GCSE/O level	12 (14.1)	12 (12.0)			
A level	13 (15.3)	22 (22.0)			
Vocational/College	17 (20.0)	14 (14.0)			
University or professional qualifications	23 (27.1)	50 (50.0)			
Age (Years)			t=0.77	193	0.443
Mean (S.D.)	28.91 (9.5)	30.02 (10.4)			

df, Degrees of freedom; GCSE, General Certificate of Secondary Education; S.D., standard deviation.

There were no significant differences between the psychosis cases and community controls in this subsample in terms of gender (χ^2=0.18, p=0.773), and age (t=-0.77, p=0.443). There was a significantly greater proportion of controls with University or professional qualifications versus cases (50% versus 27.1% respectively, p<0.001). Cases and controls with no polygenic risk score data did

not differ in terms of gender (χ^2=2.51, p=0.070), and age (t=0.34, p=0.736), compared to the subsample included in this analysis. However, controls excluded from these analyses were more likely to have University or professional qualifications compared to cases (χ^2=53.97, p<0.001). This underlines the importance of controlling for educational level in the subsequent analyses.

Childhood adversity, polygenic score, and risk for psychotic disorder

The distribution of childhood adversity together with the association with psychosis in cases and controls is shown in Table 7.2.

Table 7.2 Prevalence of childhood adversity by psychosis case status in the polygenic pilot subsample

	Cases (*N*=86) *n* (%)	**Controls (*N*=110) *n* (%)**	**Unadjusted OR**	**95% CI**	***P***	**Adjusted OR***	**95% CI**	***P***
Type of childhood adversity								
Parental separation	39 (45.9)	28 (25.4)	**2.48**	1.35-4.55	**0.003**	**2.03**	1.06-3.91	**0.034**
Parental loss	10 (11.8)	8 (7.3)	1.70	0.64-4.51	0.287	1.19	0.40-3.55	0.760
Physical abuse	14 (16.3)	15 (13.7)	1.23	0.56-2.71	0.605	1.21	0.51-2.89	0.664
Sexual abuse	12 (13.9)	9 (8.2)	1.82	0.73-4.54	0.200	2.16	0.77-6.03	0.142
Institutional care	7 (8.1)	4 (3.7)	2.34	0.66-8.30	0.185	1.68	0.45-6.27	0.439
Family arrangements	17 (20.7)	13 (14.9)	1.49	0.67-3.30	0.327	0.92	0.39-2.19	0.864
Total adversity								
1	31 (36.0)	28 (25.4)	**2.15**	1.11-4.15	**0.023**	1.72	0.85-3.50	0.133
2 or more	21 (24.4)	16 (15.5)	**2.55**	1.18-5.51	**0.017**	2.06	0.89-4.74	0.090

*Adjusted for gender, age at interview and level of education. CI, confidence interval. OR, odds ratio.

Cases were over twice as likely to report a history of parental separation compared to controls (OR=2.48, *p*=0.003) and the association held after adjusting for demographic confounders such as gender, age at interview and level of education (*p*=0.034). As expected in this small subsample, the association between childhood adversity and psychosis case status fell short of statistical significance for all the other subtypes of childhood adversity. The association with psychosis was slightly stronger for participants who reported multiple (OR=2.55, 95% CI 1.18-5.51, *p*=0.017) than single (OR=2.15, 95% CI 1.11-4.15, *p*=0.017) adverse childhood experiences. A score test for trend provided, in fact, evidence for a linear trend (z=2.72, *p*=0.006) indicating a dose-response effect for repeated adverse experiences. However, as in the main sample (Chapter 4), after adjusting for demographic confounders, the association between single or multiple childhood adversities and psychosis remained only at a trend level of significance.

Furthermore, I tested the association between polygenic risk score and psychotic disorder using a logistic regression model. As expected, higher polygenic scores significantly predicted psychosis status in this subsample (Adjusted B=16.01, 95% CI 9.22-22.10, *p*<0.001).

Gene-environment correlation

I also tested whether there was evidence for gene-environment correlation to examine the associations between polygenic scores and childhood adversity measures, adjusting for principal component and demographic confounders. Tables 7.3 and 7.4 show the results of gene-environment correlations in cases and controls, respectively.

Table 7.3 Correlation between childhood adversity and polygenic risk scores (PRS) in first-episode psychosis cases

Type of childhood adversity	*B**	95% CI	*P* value	Adjusted *B***	95% CI	*P* value
Parental separation	-4.43	-11.51-2.65	0.220	-5.33	-13.17-2.51	0.183
Parental loss	5.07	-5.75-15.89	0.359	6.43	-5.01-17.87	0.271
Physical abuse	-0.28	-9.58-9.01	0.952	-0.28	-9.83-9.27	0.954
Sexual abuse	2.93	-6.86-12.73	0.557	2.89	-7.08-12.85	0.570
Institutional care	-0.47	-12.83-11.89	0.941	0.77	-11.80-13.36	0.903
Family arrangements	2.76	-5.82-11.34	0.529	4.28	-4.69-13.26	0.349
Multiple adversities	-0.53	-7.47-6.42	0.882	-0.44	-7.96-7.07	0.908

*adjusted for principal component. **further adjusted for gender, age at interview and education level. df, degrees of freedom. *B*, regression coefficient.

In cases, higher polygenic scores were not significantly associated with parental separation (p=0.183), parental loss (p=0.271), physical abuse (p=0.954), sexual abuse (p=0.570), institutional care (p=0.903), disrupted family arrangements (p=0.349), and multiple childhood adversities (p=0.908).

Table 7.4 Correlations between childhood adversity and polygenic risk score (PRS) in controls

Type of childhood adversity	*B**	95% CI	*P* value	Adjusted *B***	95% CI	*P* value
Parental separation	-3.60	-10.22-3.01	0.285	-3.47	-10.60-3.65	0.339
Parental loss	-1.06	-11.69-9.56	0.884	0.98	-10.93-12.89	0.872
Physical abuse	0.39	-7.76-8.55	0.925	3.68	-5.27-12.64	0.420
Sexual abuse	0.89	-8.96-10.75	0.859	5.95	-5.49-17.39	0.308
Institutional care	6.33	-8.37-21.04	0.399	6.35	-8.51-21.22	0.402
Family arrangements	-1.59	-9.87-6.69	0.707	0.29	-8.37-8.96	0.947
Multiple adversities	-0.93	-6.70-4.84	0.752	0.17	-6.07-6.33	0.968

*adjusted for principal component. **further adjusted for gender, age at interview and education level. df, degrees of freedom. *B*, regression coefficient.

In controls, no evidence of correlation between polygenic risk scores and parental separation (p=0.339), parental loss (p=0.872), physical abuse (p=0.420),

sexual abuse (*p*=0.308), institutional care (*p*=0.402), disrupted family arrangements (*p*=0.947) and multiple childhood adversities (p=0.968), was found. Therefore, as hypothesized, no evidence of gene-environment correlation was found in either cases or controls.

Gene-environment interaction

Table 7.5 shows results of interactions between polygenic scores and types of childhood adversity on the presence of psychotic disorder.

Table 7.5 Interaction between childhood adversity and polygenic risk scores (PRS) in first-episode psychosis

	PRS x **childhood adversity interaction**		
Type of childhood adversity	**Adjusted RD***	**95% CI**	***P* value**
Parental separation	**0.05**	0.05-0.06	**<0.001**
Parental loss	**1.13**	1.11-1.14	**<0.001**
Physical abuse	-0.40	-1.10-0.31	0.272
Sexual abuse	**2.07**	2.06-2.07	**<0.001**
Institutional care	-1.14	-5.10-2.08	0.570
Disrupted family arrangements	0.36	-0.07-0.79	0.102
Multiple adversities	**0.14**	0.05-0.24	**0.004**

*RD adjusted for principal component, gender, age at interview and education level. CI, confidence interval. RD, risk difference.

Evidence was found for interaction as departure from additivity, indicating that the effect of polygenic risk scores on psychosis is increased in the presence of history of parental separation, parental loss or sexual abuse (*p*<0.001) and these interactions remained significant when a Bonferroni correction for multiple testing was applied (p=0.05/7=0.007). No such moderation was observed for the other types of adversity; the interaction between polygenic scores and physical abuse, institutional care and disrupted family arrangements did not reach

statistical significance. Furthermore, there was evidence of a cumulative effect of the number of adversities reported on psychosis onset moderated by polygenic risk score (p=0.004) but this did not remain statistically significant after correction for multiple testing.

Discussion

In this pilot study, I examined childhood adversity and polygenic risk for schizophrenia, and how they relate to presence of a psychotic disorder. Specifically, polygenic scores derived from a GWAS on Schizophrenia by the Psychiatric Genomics Consortium (2014) were tested for their ability to predict case/control status in this independent GAP subsample. Moreover, childhood adversity subtypes were tested for interactions with this polygenic score. Correlations between this schizophrenia polygenic score and childhood adversity were also analysed to investigate a potential gene-environment correlation.

The association between childhood adversity and psychosis was replicated in this White subsample only for parental separation and multiple adversities, whereas it did not reach statistical significance for the other subtypes of adversity such as parental loss, physical abuse, sexual abuse, institutional care and disrupted family arrangements. A direct molecular measure of genetic risk was used to show that the association between childhood adversity and psychosis is unlikely to be explained by gene-environment correlation. Moreover, results show a moderation of the association between specific subtypes of childhood adversity and psychosis by polygenic risk for schizophrenia.

Gene-environment correlation and moderation of the childhood adversity-psychosis relationship

This study focuses on polygenic risk scores to test for GxE interaction in psychosis. Within this subsample I found increased effects of polygenic risk

scores on psychosis in the presence of subtypes of childhood adversity, with evidence for interaction as departure from additivity. The interaction effects were driven by three of the six domains included in the childhood adversity measure (parental separation, parental loss, sexual abuse). Polygenic risk also moderated the effect of multiple adversities on psychosis onset, with increased dose-response effect of childhood adversities reported in those with higher polygenic risk score, though it did not withstand correction for multiple testing. Previous studies found similar interaction effects on different clinical populations. Meyers et al. (2013) observed interaction effects on smoking behaviour in adolescents between polygenic risk scores for smoking and the number of traumatic events experienced. Peyrot et al. (2014) investigated whether the effect of polygenic risk scores on major depressive disorders is moderated by childhood trauma, and found evidence for interaction as departure from both multiplicativity and additivity.

Evidence for gene-environment correlation was not found in this analysis. Polygenic scores for schizophrenia did not increase exposure to or reporting of childhood adversity in cases and controls. This is in line with my previous findings which showed that parental history of psychosis, as a proxy genetic risk factor, was not associated with greater exposure to childhood adversity in this sample.

Limitations

A number of limitations of this study need to be taken into account when interpreting the results. The sample used was underpowered to detect the likely genetic effect sizes in psychosis. I acknowledge that, the synergies described in table 7.5 are based on a sample too small to provide accurate estimates of effects and enough power to avoid false positive results (Type I error). Pilot studies do not provide useful information regarding the population effect size because the estimates are quite crude owing to the small sample sizes (Leon et al., 2011). However, as previously stated, these are exploratory analyses which I explicitly conducted as a “small-scale test of the methods and procedures to be

used on a larger scale" (Porta, 2008). The fundamental purpose of conducting this pilot study was, in fact, to examine the feasibility of a using a polygenic GxE interaction approach in psychosis in order to be replicated in a larger-scale study. The findings are indeed suggestive of potential additive interactions between a schizophrenia polygenic risk score and some forms of childhood adversity in relation to the presence of psychotic disorder and thus it would be useful to extend these findings in a much larger case-control sample.

Moreover, the participants in our sample were of White European descent, which may limit the generalisability of the present findings to samples from different ancestral backgrounds. One principal component of ancestry was included as a covariate in these analyses, as very subtle effects of population stratification at single SNPs could accumulate across the thousands of genetic variants in a polygenic score. Another limitation includes potential recall bias of childhood adversity, which has been previously discussed.

An advantage of the polygenic risk scores approach is that polygenic risk scores are based on genome-wide SNP data, although it includes the arbitrary selection of the p value thresholds for SNP inclusion and arbitrary parameters used to prune the discovery results for LD (Wray et al., 2013). However, particular aspects of the multidimensional polygenic information are lost, which could lead to biased results, for example when certain SNPs show increased effects on psychosis in the presence of childhood adversity, whereas other SNPs show decreased effects on psychosis in the presence of exposure to adversity.

Additionally, the cross-sectional design of this study limits causal inference. However, the absence of gene-environment correlations with childhood adversities both in cases and controls limits the possibility of bias from reciprocal causation. Furthermore, due to the small number of cases with both follow-up and polygenic score data available (n=71), it was not possible to investigate the interplay between risk score and childhood adversity on one-year psychosis outcomes.

Clinical applications

The liability threshold model assumes that individuals within a population possess a naturally varying liability to disease, with clinical illness only developing in those whose excess risk exceeds a certain threshold (Wray et al., 2010). In keeping with this model and only if replicated in bigger samples, the interaction effect found within this sample between polygenic risk scores and subtypes of childhood adversity in psychosis has potential implications. Polygenic risk scores might have increased effects in the presence of exposure to specific types of childhood adversity, which suggests that power in research on direct genetic effects might be larger in the presence of childhood adversity.

If replicated, these preliminary findings could be potentially translated into clinical practice, such that individuals with high polygenic risk scores might be more vulnerable to developing psychosis because of exposure to childhood adversity. In the future, this may have beneficial implications in targeting specific clinical interventions, but also in planning possible prevention programmes for individual at risk and public health strategies for psychosis. Future research should be conducted using longitudinal studies with objective prospective environmental measures collected alongside genetic data (Moffitt et al., 2005). In addition, future research could also be designed to test interaction with polygenic information applying different techniques, such as genome-wide complex trait analyses (GCTA; Yang et al., 2011; 2013). Only if replicated in bigger independent samples, such interaction effects might add a modest but important piece to the complex puzzle of psychosis's aetiology.

CHAPTER 8 – Conclusion

Overview of findings

This thesis has presented findings from a large catchment-based case-control study of childhood adversity in relation to the presence and one-year outcomes of psychotic disorder. A significant advance on previous studies was the investigation of the effect of different types of childhood adversity on clinical and social functioning of first-presentation psychosis patients followed-up over one year from initial presentation to psychiatric services. None of the previous first-presentation and chronic studies explored the interplay between family history of mental illness and different types of childhood adversity on psychosis outcomes. Moreover, no GWAS studies have investigated the possible synergistic effect of candidate genes and experiences of adversity during childhood on the course of psychosis. Finally, preliminary data were presented on a childhood adversity by polygenic risk score interaction in psychotic disorder, which is also novel in this area.

Principal findings

The original study hypotheses are restated in Table 8.1 along with a concise summary of the relevant results and an indication of whether each hypothesis was supported or not. This is followed by a more comprehensive description of the main results from each chapter. Of the 16 hypotheses made at the beginning of this thesis, only 5 were fully supported by the evidence obtained, 7 were partially supported, while no support was available for 4 of them.

Table 8.1 Summary of findings in relation to the original study hypotheses

Hypothesis	Supported?	Specific results
First-episode psychosis patients will be more likely than unaffected controls to report a history of exposure to adverse experiences during their childhood.	***Partial***	▪ Parental separation, Parental loss, and physical abuse more prevalent in patients than controls** ▪ Elevated odds ratios for institutional care, disrupted family arrangements and sexual abuse in patients but p>0.1
There will be a dose-response effect, such that psychosis cases will report greater exposure to multiple adversities than controls.	***Yes***	▪ Stronger association with psychosis in participants who reported multiple than single adverse childhood experiences, with evidence for a linear trend for association with psychosis increasing with reports of 2 or more adversities ***
Childhood adversity will be more prevalent in women than in men and in ethnic minority groups.	***No***	▪ After adjustment no interactions found for gender or ethnicity ▪ Parental separation and sexual abuse were more prevalent amongst men than women** ▪ 2 or more adversities more prevalent in men than women*** ▪ Parental separation and 2 or more adversities more common in Black African and Caribbean cases than their White British counterparts**
Childhood adversity will be more prevalent amongst patients with affective psychosis, and to a lesser extent non-affective psychosis, than controls.	***Partial***	▪ Parental Separation more prevalent amongst both affective** and non-affective*** diagnostic groups than controls ▪ Parental loss more prevalent in non-affective psychosis compared to controls**

Hypothesis	Supported?	Specific results
		▪ Stronger association of physical abuse with non-affective psychosis diagnosis than affective psychosis diagnosis**
There will be a certain degree of specificity between childhood adverse events and psychosis symptoms, such that experiences of sexual abuse will be associated with positive symptoms, experiences of physical abuse will be associated with thought disorder and cognitive disorganization symptoms.	***Partial***	▪ Sexual abuse associated with disorganized and positive symptom dimensions**
There will be a higher prevalence of childhood adversities in those controls who report psychotic-like experiences (PLEs) than in those controls who did not report PLEs.	**Yes**	▪ Parental separation, physical abuse & sexual abuse were more common in controls with than without PLEs** ▪ Trend for association with PLEs increasing with 2 or more adversities*** ▪ Elevated odds ratios for institutional care & family arrangements in controls with than without PLEs but p>0.1
History of childhood adversity will be associated with a worse clinical and social outcome amongst individuals with psychosis a year after their first contact with mental health services.	***Partial***	▪ Patients reporting physical abuse were not in a stable relationship at follow-up compared to those who did not report PA** ▪ Patients reporting a history of parental separation were more likely to have longer hospital admissions over the first year and to be non-compliant with medications at follow-up** ▪ Patients reporting parental loss demonstrated better clinical and social functioning one-year after presentation compared to those who did not

Hypothesis	Supported?	Specific results
		report parental loss***
Psychosis cases that reported exposure to multiple types of adversities will have worse clinical and functional one-year outcomes than those who did not report exposure to multiple adversities.	***No***	▪ Evidence for a linear trend for association with length of hospital admission increasing with 2 or more adversities but p>0.1
Family history of psychosis in first-degree relatives will be associated with psychosis in participants.	***Yes***	▪ Psychotic disorders were around 4 times more common in first degree relatives of cases than controls***
Parental genetic risk will partially moderate the association between childhood adversity and psychosis.	***Partial***	▪ No evidence that parental history of psychosis or mental illness more broadly attenuated the association between parental separation and psychosis*** ▪ Reports of 2 or more childhood adversities remained significantly associated with psychosis even after adjusting for parental psychosis*** ▪ But the association between parental loss and psychosis fell short of statistical significance after adjusting for parental psychosis
Participants with a family history of mental illness and reported exposure to adverse childhood experiences will be more likely to be psychosis cases than controls.	***No***	▪ No evidence of additive interaction with familial liability ▪ But stronger association with psychosis for individuals with both a family psychiatric history and parental loss
The synergistic effect of childhood adversity and familial liability will	***No***	▪ No evidence of an additive interaction between childhood adversity and family history of mental illness on one-year outcomes

Hypothesis	Supported?	Specific results
have an impact on one-year clinical and social outcomes of psychosis.		▪ But parental separation had stronger association with length of hospital admission and non-compliance with medications when no family history of mental illness was reported
Participants with at least one copy of the risk allele of the COMT, AKT1 and FKBP5 polymorphisms and reported exposure to childhood adversity will be more likely to have psychosis than participants exposed to adversity who carry the non-risk allele.	***Partial***	▪ History of parental separation and reports of two or more adversities were more prevalent amongst psychosis cases with one or two copies of the *COMT Val* allele ▪ Individuals with one copy of *AKT1* rs2494732 risk allele (‘*C*’) and a reported history of parental separation or multiple adversities had increased odds of psychotic disorder ▪ But parental separation and multiple adversities were associated with psychosis caseness in patients with no copies of the *FKBP5 rs1360780* risk allele (‘*T*’)
A gene by childhood adversity interaction model will provide a better prediction of one-year clinical and social outcomes amongst psychosis patients than either risk factor alone.	***Partial***	▪ No interaction between childhood adversity and *COMT Val158Met* ▪ But patients reporting parental separation and having one or two copies of the *COMT Val* allele showed increased risk of being non-compliant with anti-psychotic medications at one year** ▪ Evidence of an interaction between parental separation and *AKT1* rs2494732 genotype on hospital admission days***
Higher polygenic risk for schizophrenia will be associated with	***Yes***	▪ Higher polygenic risk scores significantly predicted psychosis status in

Hypothesis	Supported?	Specific results
psychosis case status in this GAP subsample.		this subsample***
The "polygenic risk score" x "childhood adversity" interaction model will better predict an individual's odds of psychotic disorder than the single candidate gene x childhood adversity interaction model.	***Yes***	▪ Evidence of additive interaction between a schizophrenia polygenic risk score and parental separation, parental loss, sexual abuse and multiple adversities in relation to the presence of psychotic disorders***

*p<0.10 non-significant trend; **p<0.05 conventionally significant; ***p<0.01 highly significant. *AKT1*, serine/threonine-protein kinase, *COMT*, catechol-O-methyltransferase gene, *FKBP5*, glucocorticoid receptor co-chaperone. *Met*, methionine. PLEs, psychosis-like experiences. *Val*, valine.

Chapter 4

The data presented in this chapter demonstrated that self-reports in adulthood of adverse childhood experiences using the CECA.Q were more prevalent in psychosis cases compared to community controls. Extensive analyses revealed that separation from father or mother for at least six months and death of a parent before the age of 17 years were the forms of adversity most robustly associated with psychotic disorder. Individuals who reported these forms of adversity had two-fold greater odds of being a psychosis case than a control. There was only a weak trend for sexual abuse, institutional care and disrupted family arrangements to be more commonly reported by psychosis cases than unaffected controls. No associations with psychosis remained for physical abuse once adjustments had been made for demographic confounders. There was evidence of a linear trend for multiple adverse experiences to be more common amongst psychosis cases compared to controls than exposure to single types of adversity. Furthermore, despite significantly higher prevalence of some forms of adversity amongst male than female participants and Black African and Caribbean than White British participants, no significant interactions with gender or ethnicity were found after adjusting for all confounders.

In terms of specific psychosis diagnoses, parental separation demonstrated associations with both affective psychosis and non-affective psychosis, whilst parental loss and physical abuse were only significantly associated with non-affective psychosis. Moreover, there was evidence of associations between sexual abuse and specific symptom dimensions, namely disorganization and positive psychosis dimensions. Further exploring such associations, stereotyped thinking and hallucinatory behaviour were associated with experiences of sexual abuse before 17 years of age. Additionally, within the control sample, separation from a parent, physical and sexual abuse and reports of two or more adversities during childhood, were more prevalent amongst those who reported experiencing at least one psychosis-like experience in the past year.

A total of 83% of the first-episode psychosis sample was followed-up over one year from first presentation to mental health services for psychosis. Patients reporting history of childhood adversity did not differ in terms of illness course, remission from psychotic symptoms for at least 30 days over one year and overall clinical functioning at follow-up. After adjusting for clinical confounders, experiences of parental loss significantly predicted lower symptom levels at 1 year. However, this could be a chance finding explained by the very small number of cases reporting parental loss included in the follow-up analyses.

In terms of social outcomes, history of physical abuse was associated with not being in a steady relationship at follow-up and experiences of parental loss significantly predicted better social/vocational functioning measured with the GAF at one year post presentation. Furthermore, parental separation was associated with longer hospital admission over the follow-up year and non-compliance with medications at one-year follow-up. No dose-response effect of childhood adversities on course of illness was found.

Chapter 5

There was no evidence of a gene-environment correlation, such that participants with a parental history of psychosis were not more likely to report exposure to childhood adversity. Controlling for parental history of mental illness did not substantially attenuate the association between childhood adversity and psychotic disorder, except for parental loss. No evidence was found for familial liability by adversity interactions in increasing the risk of psychosis onset. Moreover, there was a significant association with psychotic disorder amongst those who reported exposure to childhood parental separation, physical abuse, disrupted family arrangements and more than two adversities but no family history of mental illness.

No evidence was found for familial liability by childhood adversity interactions on the course of psychosis. Associations were evident between parental separation and length of hospitalization in participants with no family

history of mental illness. Furthermore, there was a significant association with non-compliance with antipsychotic medication at 12 months amongst those who reported exposure to childhood parental separation but no parental mental illness. Finally, there was a non-significant trend for a greater association with not being in a steady relationship amongst those who reported exposure to childhood physical abuse but no parental mental illness.

Chapter 6

The data presented in this chapter revealed no main effect of the *COMT Val158Met*, *AKT1* rs2494732 and *FKBP5 rs1360780* polymorphisms on psychosis case status or reported exposure to childhood adversity. Results from empirical analyses on a "oligogenic risk score" for *COMT*, *AKT1*, *FKBP5* genes (constructed by summing the subject's number of risk alleles by the number of genes) x childhood adversity interaction on presence of psychotic disorders showed a significant association between parental separation, total adversities and psychosis in carriers of low (up to two risk alleles) and medium (three risk alleles) oligogenic risk. Hypothesizing that the association with psychosis could be driven by the effect of single candidate genes, I subsequently explored the interplay with the selected genes. I found no interaction between childhood adversities *COMT Val158Met*, *AKT1* rs2494732 and *FKBP5* rs1360780 polymorphisms in the presence of psychotic disorder. However, participants with a history of parental separation who were carriers of two *AKT1* risk alleles were more likely to have longer hospital admissions compared to non-risk allele carriers throughout the year from first contact with mental health services for psychosis, though the interaction between *AKT1* rs2494732 and parental separation on the length of hospital stay over the one-year follow-up fell short of statistical significance after adjusting for multiple testing.

Chapter 7

Replication of the association between parental separation in childhood and psychotic disorder in adulthood was confirmed in this small subsample. However, the association between other types of childhood adversity and psychosis failed to reach statistical significance possibly due to insufficient power to detect an effect. Higher schizophrenia polygenic risk scores predicted psychosis status but no association was found with any type of childhood adversity in cases and controls. Evidence was found for interaction as departure from additivity, indicating that the effect of polygenic risk scores on psychosis is increased in the presence of a history of parental separation, parental loss or sexual abuse. A synergistic effect on psychosis caseness was also found between the number of reported childhood adversities and polygenic risk score.

Methodological issues

Sampling issues

Firstly, the cases in this thesis were all individuals presenting for the first time with psychotic symptoms, over a defined period, to the local psychiatric services. Therefore, my final clinical sample includes patients with psychotic symptoms who were experiencing an acute episode of psychosis and were a risk to themselves or others, and thus they might comprise more severe cases of psychosis than if the sample had also been drawn from community services. This has to be taken into account in interpreting the results. However, patients were well enough to complete the assessment so were not at the height of their acute episode. Moreover, as this was a first-presentation sample the potentially detrimental effects of longer-term psychosis and medication use on ability to recall information from the past were reduced. Another possible limitation is that I used the date of first contact with services for a psychotic disorder as an estimate for onset of psychotic disorders. Several studies have considered the

date of first contact with services as a proxy for date of onset of psychotic disorders (Conus et al., 2010; Decoster et al., 2011). As part of the study, information on DUP was collected from a subgroup of patients (N=175) using the Nottingham Onset Schedule (Singh et al., 2005), which estimates DUP as the number of weeks between the onset of the first psychotic symptom and first contact with mental health services. In this subgroup, I tested whether DUP was associated with reported childhood adversity. I found no difference in the mean ($t=-0.773$ (df 173), $p=0.440$) and median ($\chi^2= 0.01$ (df 1), $p=0.952$) lengths of DUP between first-presentation psychosis patients who reported any form of childhood adversity (Mean=7.3 (SD=11.56), median=2.0 weeks) and those who did not (Mean=5.9 (SD=9.8), median=2.0 weeks). Moreover, estimating the date of onset of the first psychotic symptom from patients' self-report is liable to recall bias; while the date of first contact with psychiatric services is clearly defined and represents the time when not just one but a cluster of psychotic symptoms had reached the illness threshold. Therefore, the results presented in this thesis mostly relate to individuals presenting for the first time with psychosis to psychiatric inpatient services and may not be generalisable to patients presenting to community services or those specifically in their first ever episode of psychosis.

Although efforts were made to obtain a control sample that was representative of the local community population, it was not randomly selected and thus it is possible that this may have led to erroneous findings. Previous studies comparing probability and nonprobability sampling have shown that convenient samples yielded a demographic profile similar to that produced by a general population sampling scheme (Cumming, 1990; Field et al., 2006; Smith et al., 2005). The final sample of controls used in the current analyses was similar, according to the last UK census data, on a number of socio-demographic factors, such as gender and age, to the population that the cases come from (www.statistics.gov.uk/census 2001). However, controls included in this study were more likely to be White British and with a higher level of education

compared to cases, and I controlled for these demographic characteristics in all my analyses. In the current study, the rates of childhood adversity within the control sample were similar to those found in surveys of the UK general population (Radford et al., 2013), suggesting that this aspect of the control sample is unlikely to have affected the results. Controls were also administered the Psychosis Screening Questionnaire (PSQ) (Bebbington & Nayani, 1995) and excluded if they screened positive for psychotic disorder. However, we did not screen for other mental health problems and thus it is possible that some of the controls would have been experiencing common mental health problems such as depression which may have affected the results. Nonetheless, this may have made the comparisons more conservative and is likely to have produced a more representative sample of the general population.

However, it was not possible to completely rule out the possibility that data on childhood adversity were missing not at random as it was not possible to account for systematic differences between the missing values and the observed values using the observed data (Sterne et al., 2009). For example, individuals that experienced adversity in childhood may be more likely to refuse to respond to the CECA.Q. In these circumstances, specialist methods to address missing data may reduce the loss of precision and power resulting from exclusion of individuals with incomplete predictor variables but are not required in order to avoid bias. When data are missing not at random, bias in analyses based on multiple imputation may be as big as or bigger than the bias in analyses of complete cases (Sterne et al., 2009).

Design issues

This thesis involved data collected cross-sectionally thus preventing any causal interpretation of the findings from being made. It was not possible to infer whether exposure to adverse childhood experiences increased the risk for psychosis or whether having prodromal symptoms or psychotic experiences in childhood or early adolescence might have increased the risk of exposure to

childhood adversity. Indeed, an existing longitudinal study of adolescents suggests that there may be a bidirectional relationship between physical assault and psychosis-like experiences (Kelleher et al., 2013). However, when they controlled for this bidirectionality they still found that physical assault strongly predicted psychosis-like experiences. Nonetheless, it would be ideal to conduct longitudinal studies of the childhood adversity and psychotic disorder association to better ascertain the temporal order of exposure and outcome. There are practical problems inherent in this design though when the outcome of interest is fairly rare. Therefore, retrospective assessment is commonly used in studies investigating the role of childhood risk factors in clinically-relevant psychiatric disorders as it avoids the high expense associated with following up a very large number of participants over several decades.

Issues regarding measurement of adversity

Another consequence of using a cross-sectional design with adults is the reliance on retrospective assessment of adverse childhood experiences. Events recalled from a long time ago may be affected by processes of forgetting (Halverson, 1988; Piolino et al., 2002), depressed mood (Lewinsohn & Rosenbaum, 1987; Wolfkind & Coleman, 1983), infantile and traumatic amnesia (Feldman-Summers & Pope, 1994; Lewis 1995), subsequent events (Rovee-Collier, 1990) and a need to justify or understand mental illness (Gerlsma et al., 1990; Schacter, 2001). These might also be amplified by the cognitive impairments (Saykin et al., 1991), delusional beliefs (Howard, 1993; Young et al., 2001) and detachment from reality associated with psychosis (Lysaker et al., 2005).

However, it has been indicated that histories of childhood adversity obtained retrospectively from psychosis patients showed evidence of reasonable reliability and comparability (Fisher et al., 2011). Specifically, reports of adversity seem to be stable over a long period of time (7 years) and do not appear to be significantly influenced by current psychopathology. Furthermore, reports of

adversity occurring during childhood are similar when obtained by different assessment instruments, and childhood abuse documented in clinical case notes is also self-reported on a questionnaire (Fisher et al., 2011). Moreover, death or separation from a parent, are events, due to their strong objective framing within the individual's surrounding community, that are much less liable to recall bias than, for example, sexual abuse or other 'shame-secret' traumas (Shatzow & Herman, 1989).

Furthermore, in the current study we attempted to improve the likelihood of eliciting histories of adversity by using a questionnaire that includes screening questions which are followed up with more detailed probes to obtain more concrete details of exposure (Bifulco et al., 2005). We also used the questionnaire as a face-to-face interview with each participant, rather than them completing it themselves. All of these factors increase the likelihood of an individual accurately remembering past adverse experiences (Hardt & Rutter, 2004). However, using the most conservative cut-points may have led to an under-estimation of the actual prevalence of adversity. This is likely to be less problematic than over-estimating the prevalence. It also makes sense to focus on the more severe forms of childhood adversity as these tend to be reported more accurately (Hardt & Rutter, 2004) and may be more likely to have a psychological and biological impact upon the child that might lead to the development of psychosis.

Another possible limitation is that a shortened version of the CECA.Q (Bifulco et al., 2005) was employed to retrospectively assess the presence and severity of a range of adverse experiences prior to 17 years of age. The full CECA.Q includes 7 sections. Cases and controls in the GAP study only completed 4 of the 7 main sections: sections 3 (maternal antipathy and neglect), 4 (paternal antipathy and neglect) and 5 (support figures) were left out of the GAP assessment battery due to time constraints. Moreover, utilising a more in-depth interview would have been preferable to obtain more details of the adversities. The complete version of the CECA takes the form of a semi-structured interview,

which aims to reflect objective features of early life experience with probing questions to ascertain details of context and time-sequence of experience. However, the interview takes an average of 2 hours to administer for a medium risk case and around three times as long to transcribe and score. Therefore, the full CECA interview was not feasible to include within an assessment battery that was already several hours long.

Alternatively, others have suggested that face-to-face interviews could result in under-reporting of early adversity. It may be embarrassing for respondents to disclose abuse when questioned in person (Femina et al., 1990; Gilbert, 1988) and victims of childhood sexual abuse are usually very reluctant to tell anyone about it (Read et al., 2007). Previous studies found that the average time before disclosure by individuals who had suffered childhood sexual abuse was between 9.5 years and 16 years (Frenken & Van Stolk, 1990; Anderson et al., 1993; Read et al., 2006). This has led to suggestions that anonymous questionnaires may be more likely to elicit abuse histories than face-to-face interviews respecting confidentiality (Dill et al., 1991). Thus in the current study, which involved face-to-face assessment, it is possible that not all instances of adverse experiences were reported.

Issues regarding the role of confounding

A potential confounder of the association between childhood adversity and psychosis may be represented by socio-economic disadvantage. Socio-economic disadvantage (SES), conceptualised as reported difficulty in affording basic necessities (e.g. heating, food), is a multi-dimensional concept that includes accessibility to valued commodities such as wealth, parental educational level, occupational prestige, social influence and cultural resources (House, 1981; Mueller & Toby, 1981).

A considerable amount of epidemiological literature has reported associations between SES and mental disorders, from attention deficit hyperactivity disorder in childhood to alcohol dependence and mood disorders in

adulthood (Aro et al., 1995; Gilman et al., 2002; Keyes & Hasin, 2008; Murphy & Barkley, 1996; Russel et al., 2015). Many studies have focused on the risk for schizophrenia in those with lower SES (Dohrenwend et al., 1992; Samele et al., 2001; Werner et al., 2007). Furthermore, they have noted that schizophrenia patients with low SES may be more likely to be exposed to stressful life events.

From a developmental perspective, the social class of one's parents and the environmental dis/advantages one experiences construct important preconditions for individuals' coping with daily problems (McLoyd, 1998). Lower-SES children experience more negative life events (stressors) than higher-SES individuals; in addition, they perceive greater negative impact from any given event (stress appraisal), they are more likely to experience negative emotions such as depression and anxiety, and to be more hostile and less optimistic about their future than higher-SES individuals are (Chen, 2004). These pathways could explain the effect of SES on mental health. Furthermore, SES has also shown significant associations with the course of other psychiatric illnesses. For example, Gilman et al. (2003) found that the increased risk of depression among individuals from lower SES backgrounds persisted in adulthood and predicted an increased risk for recurrent episodes.

A significant association has also been found with clinical psychotic symptoms, which showed group differences in those with lower versus higher SES after a 1-year follow-up (Won Hur et al., 2015). In term of social outcomes, a potential interplay between child/adolescent SES and adult employment with regard to adult health has been consistently noted in the literature (for example, Adler & Rehkopf, 2008; Berkman, 2009; Bowes et al., 2013; Braveman & Barclay, 2009; Kawachi et al., 2010). In particular, Ross and Mirowsky (2011) suggest that negative change in an individual's own SES attained during adulthood might have a more detrimental impact on health outcomes for those from low SES families of origin. Given that these individuals are initially equipped with fewer resources, their own attained SES and its accompanying resources are the primary source for maintaining and/or improving health. Following this logic, it is plausible that

the impact of unemployment, an indicator of attained SES, on those with childhood adversity and psychosis might be exacerbated among those from lower SES families of origin.

However, despite evidence that socio-economic status may confound the association between childhood adversity and psychoses and its outcomes, other studies have suggested instead that SES only plays an indirect and marginal role in the onset of full-blown psychosis (Kirkbride et al., 2008). A potential explanation is that a low SES of either the individual or the parents may be a ramification of having a mental disorder and not a preceding factor of these disorders (Goldberg & Morrison, 1963; Jones et al., 1993).

I am aware that parental socio-economic status at birth of the individual would have provided a better confounder of the relationship between childhood adversity and psychosis, as well as its clinical and social outcomes, but this variable was not routinely collected for cases and controls in the GAP study. However, I investigated the confounding effect of family history of mental illness (which could be considered a very crude proxy for family SES) in the association between childhood adversity and psychosis in Chapter 5 and results showed that the association remained significant for parental separation and total adversities. However, this does not completely rule out the possibility that SES may have an impact on the findings presented in this thesis had it been possible to control for it.

Follow-up assessment issues

Information on clinical and social course of psychosis during the year after first presentation to mental health services was collected retrospectively with the Global Assessment of Functioning scale (Endicott et al., 1976) and the Follow-up Psychiatric and Personal History Schedule (Jablensky et al., 1992), a standardized guide developed by World Health Organization for historical data collection. I completed the measures using the South London and Maudsley NHS Foundation

Trust (SLAM) Patient Journey System (PJS), an integrated electronic clinical records system used across all Trust services.

One issue with this method of data collection is the potential for information bias. Ratings of presence or absence of symptoms were made on the basis of clear and definite information in the clinical records. It is possible that periods of remission or information on overall clinical functioning were over-estimated or underestimated as patients do not always disclose symptoms to clinicians and clinicians do not always accurately record what patients say. Additionally, many different healthcare professionals were involved in patient care, so the measurement of outcomes throughout the database would probably be less accurate and consistent than that achieved with a prospective cohort study design (Sedgwick, 2014). More detailed information about symptoms fluctuation and social functioning could have been obtained using interviews directly with the patients but insufficient funds were available to conduct these interviews at one year. This urges caution in interpreting my results.

The use of only two time-points for assessment just one year apart meant I was unable to get a detailed picture of the association between childhood adversity and trajectories of psychosis illness course over a longer period of time or social/vocational outcomes several years after initial presentation. It is unknown whether childhood adversity may have a more substantial impact on the longer-term course of psychosis than was evident in the reasonably short period considered within this study. For instance, in depression, childhood adversity has been shown to be associated with persistent or recurrent depressive episodes (Nanni et al., 2012) particularly in interaction with genetic risk (Brown et al., 2013; Uher et al., 2011). It is possible that similar effects may be seen in psychosis but were not detectable in one-year timeframe utilised in the current study.

Moreover, only association and not causation can be inferred from the results as it was not possible to measure and then control for, through statistical analysis, all factors that may have affected the outcome nor would it have been

ethical to randomly allocate individuals to different adversity exposures. However, there are some advantages of retrospective cohort studies, such as requiring less time to complete and allowing the analysis of multiple outcomes simultaneously (Sedgwick, 2014).

Another methodological caveat of this follow-up is the problem of selection and information bias arising from loss to follow-up and missing or inaccurate data. In an attempt to minimise attrition, I was exhaustive in my efforts to trace cases and to establish deaths and emigrations. The whereabouts or status of over 90% of the cohort was determined. However, around 15% of individuals recruited to the study did not have complete information for the one-year follow-up; as there was no evidence that they differed significantly at baseline from those on whom data was obtained this suggests that attrition is unlikely to have seriously affected my findings.

Furthermore, it was not possible to accurately extract from electronic records data on clinical symptoms, such as depression and anxiety, which have been shown to be associated with childhood adversity and psychosis (Bifulco et al., 1991; Fisher et al., 2012). Anxiety and depression are both associated with paranoid ideation and auditory hallucinations (Freeman et al., 2011) and people with anxiety and depressive disorders are more prone to psychotic-like experiences (Varghese et al., 2011). Furthermore, affective instability and worry are both strongly associated with psychosis, with the possibility that this may be responsible for fluctuations (Marwaha et al., 2014) and persistence of psychotic symptoms (Freeman et al., 2013). Unfortunately the recording of these symptoms in the clinical records was very sparse and no assessments were conducted during the baseline GAP study either. Therefore, it is unknown whether some of the findings presented in this thesis could have been due to the presence of depression or anxiety amongst the psychosis cases who have been exposed to childhood adversity.

Issues concerning assessment of genetic risk

Another issue is that information collected from the FIGS might not represent the true family history of psychosis and mental illness. Little can be inferred from a negative family history, as this is likely to include undeclared, unknown or as yet unexpressed positive family history of mental illness (Farmer et al., 1990). In order to reduce such bias, for psychosis cases the FIGS interview was supplemented by information retrieved from clinical records but again these may still miss familial cases and such notes were not available for controls. Family psychiatric history also captures familial effects of non-genetic origin (van Os et al., 2008). However, the shared familial (non-genetic) component of schizophrenia risk is estimated to account for just a small proportion of the overall trait variance (4.5% to 11%; Lichtenstein et al., 2009).

In addition, a limitation of gene-environment interplay research is the proneness to false positive results. In fact, statistical interactions found in the current study could be due to the choice of a specific model for interaction testing rather than a real biological phenomenon (Clayton & McKeigue, 2001; Danese, 2008; Thompson, 1991). Another issue with the GxE analyses conducted in this thesis, is that the sample size was underpowered to detect interaction effects. Data were only available on 285 psychosis cases and 256 controls with completed CECA-Q. A QUANTO power calculation revealed that 340 patients and 340 controls would be required to obtain 80% power for detection of GxE interaction, with a minor allele frequency of 0.5 and a significance level of 0.050. Thus my sample lacked power and this may explain why more GxE interactions were not found.

A final major limitation is the amount of multiple testing conducted in this thesis given the size of the sample employed. Reasonably liberal *p* values to assess statistical significance were considered as only small numbers of individuals were expected to have been exposed to some forms of adversity, so that effects were not missed. However, despite several odds ratios were elevated they failed to reach conventional significance levels indicating that the

study was underpowered to detect such effects. Conversely, as a large number of analyses were completed it is probable that some of the significant findings reported were in fact spurious associations. Therefore, replication of the results from this thesis is required in larger, epidemiologically-based samples and meanwhile the current findings should be considered as extremely tentative. This is particularly true of the pilot results in Chapter 7 which were based on a very small sample of White descendants. This further limits the generalisability of the preliminary evidence of a polygenic risk score by environment interaction.

Clinical implications

During recent years, the reductionistic 'biogenetic' paradigm that dominated mental health services and research (Bentall, 2003; Read et al., 2004) has been overshadowed by the necessity to focus on the psychosocial causes of mental health problems (Read & Bentall, 2012). The high prevalence of childhood adversity amongst those experiencing psychotic symptoms, in individuals at ultra-high-risk of psychosis and in patients with full-blown psychotic disorders (Addington et al., 2013; Arseneault et al. 2011; Bebbington et al., 2004; Bechdolf et al., 2010; Morgan et al. 2007; Fisher et al. 2010; Kelleher et al. 2013; Phillips et al., 2012; Thompson et al., 2010; Trotta et al. 2013) emphasizes the need for early intervention programs to focus on these events, for example by screening for childhood adversity, and offering specific treatment to reduce the high levels of emotional arousal and distress which results from the experience of early adversities. This is particularly relevant to the findings presented in this thesis which showed a robust association between parental separation or loss and both psychosis and psychosis-like experiences, with the magnitude of such association increasing in those reporting multiple adversities. Therefore, it is imperative that clinicians enquire routinely about childhood adversities when they try to assist people experiencing psychotic experiences or clinically-relevant psychotic disorders.

However, victims of early adversity are typically reluctant to disclose their histories of abuse and practitioners often struggle to know where to refer patients if they do disclose (Young et al., 2001). Little childhood abuse is identified by mental health workers in routine practice (Read & Fraser, 1998; Lothian & Read, 2002) but when people are asked about these experiences, disclosure rates rise dramatically (Read & Fraser, 1998). Therefore, training for staff is necessary and guidelines for why, when, and how to ask, have been recently published (NHS Confederation, 2008; Read, 2006; Read et al., 2007). Clinicians should routinely ask about history of adversity, especially occurring during the client's childhood in order to provide appropriate support and therapy (Auckland District Health Board, 2000). Several well-validated screening tools for childhood adversity, such as the Traumatic Event Screening Instrument, are freely available online through the National Center for PTSD (http://ptsd.va.gov) and the National Child Traumatic Stress Network (http://NCTSN.org). These tools allow clinicians to perform a brief risk assessment and evaluation (Gerson & Rappaport, 2013), though information for clinicians on where to refer patients who have been traumatised for appropriate support and treatment is also essential.

Given the higher prevalence of childhood adversities reported by first-episode psychosis cases and community controls experiencing PLEs in this sample, psychotherapies focused on childhood adverse experiences should be taken into account for the treatment of clinical and sub-clinical psychosis symptoms, as they have been shown in randomized controlled trials to be effective compared with more general or unstructured therapies (Cohen et al., 2010). A range of evidence-based psychological and psychosocial treatments are available for psychosis (Read et al, 2004), including cognitive (Morrison, 2009), psychodynamic (Rosenbaum & Summers, 2013) and family therapy (Aderhold & Gottwalz, 2004). These should be offered to everyone experiencing psychotic phenomena (Read & Ross, 2003; NICE, 2009) and tailored specifically with

trauma-focused components for those who have also suffered childhood adversities (Mueser et al., 2004; Larkin & Morrison, 2006; Smith et al., 2006).

Moreover, without considering past exposure to adverse experiences, the efforts to engage and treat psychosis patients may be unsuccessful (Grella & Joshi, 2003). A factor most commonly claimed to have a causal effect on outcome is the therapeutic alliance (TA), defined as the quality of the relationship between therapist and client, characterised by trust and a sense of common purpose (Wampold, 2001). This is also relevant to the findings presented in this thesis, which indicate that individuals separated from parents during childhood have poor compliance with medications and longer hospital stay, and those reporting physical abuse are more likely to be not in a relationship. Therefore, given the powerful effect of experiences of early victimization in creating mental representation, negative beliefs and attributional biases (Campbell & Morrison, 2007; Fisher et al., 2012; Fowler et al., 2012), people with histories of childhood adversities may have more difficulties in trusting others, especially authority figures such as health professionals (Lecomte et al., 2008; Mueser et al., 2002). Individuals with traumatic childhood experiences have shown specific difficulties in seeking help and in maintaining relationships (Berry et al., 2007; Pearlman & Courtois, 2005), with higher rates of avoidance and discomfort with closeness specific to individuals with a first episode of psychosis compared to non-clinical controls (Couture et al., 2007). Because of such difficulties, patients with a history of childhood adversity might be difficult for mental health professionals to reach to establish a good therapeutic alliance (Goldsmith et al., 2015) and this, in turn, might prolong the time spent on a psychiatric ward and/or reduce compliance with treatments, including medication.

Furthermore, given the strong association found between family history of mental illness and psychosis in this sample, interventions focused on helping parents with psychosis and other severe mental health problems to develop better relationships with their families and/or providing family education and

support could improve their children's attachment relationships and in turn, help children develop more positive relationships with others in adulthood (Mathews et al., 2014). If the caregiver is perceived as unavailable, unresponsive and insensitive, this could lead to the development of an insecure attachment style in the child and to the child experiencing difficulties in relating to others (Mathews et al., 2014). Involving parents in treatment is more effective than treating the patient alone (Cohen et al., 2010) and is likely to be beneficial with psychosis patients who have experienced adversity (though may not be appropriate if the parent was an abuser).

In recent years, virtual reality (VR) techniques have demonstrated that psychotic symptoms could be elicited both in patients with psychotic disorders and healthy individuals (Freeman et al., 2005). Therefore, another strategy is the use of VR as diagnostic instrument to test whether individual exposure to certain environments is associated with psychotic interpretations in individuals with higher polygenic risk, which I found to interact with childhood adversity in psychosis onset in the current sample. VR might also represent a useful first approach in the treatment of individuals at risk to develop psychosis by providing a safe environment for initial therapeutic work (Veling et al., 2014). Recent work in the field of 'Therapygenetics', namely the role of genetic predictors in response to psychological treatment interventions, has shown some evidence in relation to mood and anxiety disorders (Eley et al., 2012; Lester & Eley, 2013). Therefore, testing for the association between polygenic risk x childhood adversity in treatment outcomes of psychosis would be a useful avenue for future research and it may help with targeting interventions to vulnerable individuals in order to maximize their effectiveness (Moffitt et al., 2005).

The outcome of psychosis is not simply related to a single initial factor but it is the result of complex lifelong interactions between numerous biological and psychosocial factors (Ciompi, 1988; Wieselgren et al., 1996). Our goal must be to better understand and identify these factors in order to treat the patients more optimally from the very beginning. As I tried to demonstrate with this

work, the prognosis of psychosis, at least in the short-term, is not hopeless, since quite a large number of patients have a good overall outcome at one year. However, further research is needed to identify the patients belonging to the group with good as well as with poor outcomes at an early phase of the disorder in order to target resources more effectively.

Directions for future research

I acknowledge that using a cross-sectional method of data collection may lead to recall bias and that the ideal design would be a prospective follow-up study. However, this is not feasible in relation to clinically-relevant psychotic disorders as these only occur in approximately 3% of the population (van Os et al., 2009) and the period of risk for developing them extends to 40 years of age or more (Hafner et al., 1993). Thus tens, if not hundreds, of thousands of individuals would need to be followed up for at least four decades to enable such associations to be robustly assessed prospectively which would not be financially viable.

Prospective studies are possible for psychotic-like experiences, which are more prevalent in the general population, and several studies have looked at how childhood adversity is associated with such sub-clinical experiences (Arseneault et al., 2011; Kelleher et al., 2013; van Nierop et al., 2014a). However, it is unclear whether such findings can be extrapolated to clinical psychotic disorders as the majority of individuals who have psychotic-like symptoms do not develop psychotic disorders (Fisher et al., 2013), indicating that there may be some differences in aetiology. Therefore, it was not feasible for me to collect data on childhood adversity prospectively in a birth cohort as the numbers required to obtain a sufficient number of cases would be too large to be cost-effective.

A random sample of controls representative of the entire population, rather than a convenient sample, would have also been preferable for this type

of study. Convenience samples are used because they are easier to recruit and thus the costs are lower, but they are likely to yield biased results.

The use of different instruments to obtain more details of the adversities was not feasible within an assessment battery that was already several hours long. Therefore, if time had permitted it would have been preferable to conduct a more in-depth interview, such as the full Childhood Experience of Care and Abuse interview (Bifulco et al., 1994), with participants to obtain more detailed information about their experiences and potentially improve the accuracy of reporting (Hardt & Rutter, 2004). This would allow investigation of the timing of exposure as well as relationship to perpetrators of childhood maltreatment and re-victimization. Moreover, the use of more extensive interview assessment would also have allowed coverage of a wider range of life events, focusing not only in childhood, such as being the victim and/or perpetrator of bullying (Bebbington et al., 2004; Campbell & Morrison, 2007; Hardy et al., 2005; Kelleher et al., 2008; Lataster et al., 2006; Nishida et al., 2008; Tachibana, 1990; Trotta et al., 2013), witnessing domestic violence (Bebbington et al., 2004; Kelleher et al., 2008) and psychological or emotional abuse (Berenbaum et al., 2003; Colins et al., 2009; Compton et al., 2004; Rubino et al., 2009; Whitfield et al., 2005), which have all been demonstrated to be associated with psychotic disorders or psychosis-like symptoms.

Face-to-face interviews would have been preferable for the assessment of more detailed clinical and social/vocational functioning over the first year of psychosis. Face-to-face interviews would also allow collection of information on other psychiatric comorbidities shown to be associated with childhood adversity, such as PTSD (Mueser et al., 1998, 2002; Schmid et al., 2013) and personality disorder (Carr et al., 2013; Johnson et al., 1999; Golier et al., 2003; Ogata et al., 1990; Zanarini et al., 1989) that could have potentially accounted for the associations reported with psychosis. Self-harm and suicidal behaviors are also prevalent amongst victims of adversities in childhood (Fisher et al., 2012, Ford & Gómez, 2015) and would be useful to assess in future studies. Furthermore, the

pathway between childhood adversity and later onset of psychosis as well as illness course it is likely to be mediated by affective components, such as depression, anxiety, mood instability (Marwaha et al., 2014; Marwaha & Bebbington, 2014) and this could be considered on future research in this area.

Moreover, data on clinical psychotic symptoms available at different time-points stretching back into adolescence and forward further into adulthood, would allow tentative inferences to be made concerning potential trajectories in the prodromal phase as well as after the illness onset. Indeed, trajectory-based analyses are more robust to occasional misreporting or temporary fluctuations in a condition compared to data collected at a single time-point (Willett & Sayer, 1994; Wang & Bodner, 2007). It would also be useful to explore the questions addressed in this thesis with an epidemiological sample over a longer period of time as worse outcome in terms of persistence of symptoms and poorer psychosocial functioning similar findings might well be expected over a longer-term follow-up. A 10-year follow-up of psychosis cases with same inclusion criteria (Morgan et al., 2014a) as the GAP study has been conducted so it would be interesting to replicate and extend the hypotheses in this thesis in the future. Therefore, replications on large epidemiologically characterized sample of first-episode cases of all psychoses, has the potential to provide novel insights into the nature and determinants of long-term trajectories and outcomes.

Additionally, as only trauma occurring during childhood was investigated in this study, it is possible that other environmental risk factors such as cannabis use (Di Forti et al., 2009) or trauma occurring in adulthood (Beards et al., 2013) might demonstrate stronger associations with psychotic disorder and confound this relationship. Unfortunately, there was insufficient information within the GAP study to explore the role of adversity in adulthood in potentially modifying the childhood adversity–psychosis association. Ideally, future studies with larger samples would allow for the inclusion of several environmental variables in the same model, such as cannabis use and preceding or subsequent adversity, in

order to address this issue comprehensively and to obtain a greater understanding of psychosis aetiology.

Further investigation of this possible interaction in a larger sample would shed light on the validity of this supposition. Additionally, the very tentative finding in the pilot study of a childhood adversity by polygenic risk score interaction in psychosis limited just to those of White European descent would also be interesting to explore in an epidemiological sample that have polygenic scores data of each individual ethnic group to determine if this interaction varies by ethnicity. Validation of PRS on Black minority group is currently underway so there should be an opportunity to explore these hypotheses in the future in a bigger sample and also on psychosis outcomes. Additionally, it would also be important to better understand the role of epigenetic changes, namely modifications to the regulation of genes that can influence gene expression independently from DNA sequence, in risk stratification (Mill & Petronis, 2007). Epigenetic signatures have been shown to differ between individuals exposed to childhood adversity (Ouellet-Morin et al., 2013) as well as between individuals with and without schizophrenia (Dempster et al., 2011). Thus it is possible that epigenetic mechanisms may mediate the association between childhood adversity and psychosis.

Final conclusion

This thesis has identified a very specific association between parental separation or multiple adversities with psychotic disorder that is reasonably robust to the potentially confounding effects of demographic factors and family psychiatric history. The impact of childhood adversity on clinical and social functioning over the first year since contact with mental health services did not show consistent evidence of association.

Interactions between childhood adversity and genetic polymorphisms that are considered to play a role in biological sensitivity to stress were also

explored. Results did not confirm the presence of a GxE interaction on both psychosis onset and one-year outcomes. However, interaction with a schizophrenia polygenic risk score might be a better model to test for this association and a pilot investigation found an interaction with parental separation or loss and sexual abuse in relation to presence of psychotic disorder.

Replication of these findings is clearly required in larger samples conducted in different geographical locations and utilising a more robust epidemiological design with comprehensive assessments of childhood adversity, psychosis and its outcomes. A wider range of potential biological, psychological and social mechanisms need to be investigated with a particular focus on the interplay between them during development.

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APPENDIX I - List of publications related to this thesis

Journal articles

Trotta, A., Murray R.M., Fisher, H.L. (2015). The impact of childhood adversity on the persistence of psychotic symptoms: a systematic review and meta-analysis. *Psychol Med*, *45(12)*, 2481-2498.

Trotta, A., Murray, R.M., David A.S., Kolliakou A., O'Connor, J., Di Forti M., Dazzan, P., Mondelli, V., Morgan, C., Fisher, H.L. (2015). Impact of Different Childhood Adversities on One-Year Outcomes of Psychotic Disorder in the GAP study. *Schiz Bull*, doi:10.1093/schbul/sbv131.

Trotta, A., Di Forti, M., Iyegbe, C., Green, P., Dazzan, P., Mondelli, V., Morgan, D., Murray R.M., Fisher, H.L. (2015). Familial risk and childhood adversity interplay in the onset of psychosis. *BJPsych Open*, *1*, 6–13.

Abstracts

Trotta, A., Di Forti, M., Iyegbe, C., Kolliakou, A., O'Connor, J., Dazzan, P., Pariante, C., David, A, Murray R., Fisher, H. (2014). Interplay between childhood adversity and familial risk in the onset and the course of psychotic disorders. *Early Interv Psychiatry*, *8(S1)*, 138.

Trotta, A., O'Connor, J., Kolliakou, A., Di Forti, M., Dazzan, P., Pariante, C., David, A, Murray R., Fisher, H. (2014). Can childhood adversity predict onset and clinical outcomes of psychotic disorders? *Schizophr Res*, *153* (1), S374.

Stilo, S., Di Forti, M., Gayer-Anderson, C., Hubbard, K., Reininghaus, U., **Trotta, A.**, Beards, S., Fisher, H., Mondelli, V., Murray, R., Morgan, C. (2014). The joint effect of social adversity in childhood and in adulthood on predicting psychosis. *Schizophr Res*, *153* (1), S91.

Trotta, A., O'Connor, J., Di Forti, M., Dazzan, P., Pariante, C., David, A, Murray R., Fisher, H. (2013). Is childhood adversity associated with the clinical and social course of schizophrenia? Preliminary data from a one year follow-up study. *Schizophr Bull*, 39 *(1)*, S306-307.

APPENDIX II – Trotta et al. (2015a) paper

Trotta, A., Murray R.M., Fisher, H.L. (2015a). The impact of childhood adversity on the persistence of psychotic symptoms: a systematic review and meta-analysis. *Psychol Med, 45(12), 2481-2498.*

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REVIEW ARTICLE

The impact of childhood adversity on the persistence of psychotic symptoms: a systematic review and meta-analysis

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Background. Evidence suggests that childhood adversity is associated with the development of psychotic experiences (PE), psychotic symptoms and disorders. However, less is known regarding the impact of early adversity on the persistence of PE and clinically relevant psychosis. Thus we conducted a systematic review of the association between childhood adversity and the course of PE and symptoms over time.

Method. A systematic search of Medline, EMBASE and PsychINFO databases was undertaken to identify articles published between January 1956 and November 2014. We included studies conducted on general population samples, individuals at ultra-high risk (UHR) of psychosis, and patients with full-blown psychotic disorders. A meta-analysis was performed on a subgroup.

Results. A total of 20 studies were included. Of these, 17 reported positive associations between exposure to overall or specific subtypes of childhood adversity and persistence of PE or clinically relevant psychotic symptoms. A meta-analysis of nine studies yielded a weighted odds ratio of 1.76 [95% confidence interval (CI) 1.19–2.32, $p<0.001$] for general population studies and 1.55 (95% CI 0.32–2.77, $p=0.007$) for studies conducted using clinical populations.

Conclusions. The available evidence is limited but tentatively suggests that reported exposure to adverse events in childhood is associated with persistence of PE and clinically relevant psychotic symptoms. This partially strengthens the case for addressing the consequences of early adversity in individuals presenting with psychotic phenomena to improve long-term outcomes. However, the heterogeneity of studies was high which urges caution in interpreting the results and highlights the need for more methodologically robust studies.

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Key words: Adversity, course, meta-analysis, persistence, psychosis, psychotic symptoms.

Introduction

The term 'childhood adversity' is a broad concept which includes child maltreatment (all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation), peer victimization (e.g. bullying), experiences of parental loss and separation, war-related trauma, natural disasters, and witnessing domestic or non-domestic violence (Butchart *et al.* 2006). About a third of the general population has a lifetime history of childhood adversity (Kessler *et al.* 2010) and this is associated with poorer emotional wellbeing, self-harm, suicidal ideation and delinquent behaviour (Radford *et al.* 2011). Adverse childhood events also have strong associations with almost all psychiatric disorders at all life-course stages (Green *et al.* 2010). Over the past decade, increasing interest has been shown in the relationship between childhood adversity and risk of experiencing psychotic experiences (PE) in adolescence as well as full-blown psychotic disorders in adulthood (Bebbington *et al.* 2004; Morgan *et al.* 2007; Fisher *et al.* 2010; Arseneault *et al.* 2011; Kelleher *et al.* 2013; Trotta *et al.* 2013). Several reviews and meta-analyses have attempted to synthesize and quantify the magnitude of the association with onset of psychosis (Read *et al.* 2005; Morgan & Fisher, 2007; Bendall *et al.* 2008; Schäfer & Fisher, 2011; Varese *et al.* 2012). However, the potential long-lasting impact of traumatic early experiences on the course of PE and clinical psychotic symptoms remains a topic of controversy.

General population studies have suggested that childhood adversity may be associated not only with

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development but also with persistence of psychotic PE and higher symptom levels (Cougnard *et al.* 2007; De Loore *et al.* 2007; Wolke *et al.* 2013). For instance, Thapar *et al.* (2012) reported that children with persistent PE have been shown to be more likely to come from adverse backgrounds and have disturbed childhood development compared to those with more transient PE. A recent meta-analysis (Linscott & van Os, 2013) concluded that around 20% of individuals with PE continue to have these experiences over time and the longer that PE persist for the greater risk of transition to psychosis has been shown to be (Dominguez *et al.* 2010). Thus factors which predict persistence of PE are of particular interest for prevention of psychotic disorder. Moreover, studies focusing on the course of clinically relevant psychotic disorders have demonstrated that victims of childhood adversity have poorer outcomes characterized by a higher number of suicide attempts, earlier onset of psychosis, and poor medication adherence (Garno *et al.* 2005; Lecomte *et al.* 2008; Alvarez *et al.* 2011). However, findings are mixed concerning the impact of childhood adversity on the course of psychotic symptoms (Kim *et al.* 2006; Davidson *et al.* 2009; Gil *et al.* 2009; Newman *et al.* 2010; Cohen *et al.* 2012). Therefore, despite some evidence suggesting that childhood adversity is related to heightened symptom levels (Ross *et al.* 1994; Heins *et al.* 2011), it is still not clear what the impact is on the evolution of psychotic symptoms over time.

This study presents a systematic review of the available empirical literature, examining the impact of childhood adversity on persistence of PE and clinically relevant psychotic symptoms, focusing on trajectories of change in PE, transition to first-episode psychosis (FEP), and the course of psychotic symptoms after illness onset over time. In order to incorporate symptom trajectories at different levels of the hypothesized psychosis continuum, we focused on studies utilizing general population samples, individuals at ultra-high risk (UHR) of psychosis, patients with FEP, and patients with chronic psychosis.

Method

Literature search and selection criteria

We followed the PRISMA statement guidelines for systematic review and meta-analysis in this study (Moher *et al.* 2009). A systematic database search from 1 January 1956 up to 30 November 2014 was performed on Medline (PubMed), EMBASE and PsychINFO databases using search terms related to: (1) childhood adversity, (2) psychosis and (3) course of PE and psychotic symptoms, using the Boolean operator 'and' (full list provided in online Supplementary Material).

Studies were included if (*a*) they assessed adverse events in childhood, (*b*) follow-up yielded outcome data (in the PE and psychotic symptom domains), and (*c*) they were published in English in peer-reviewed journals. Studies were excluded if (*a*) they assessed adverse events that only occurred in adulthood, (*b*) the study involved a clinical sample that included organic aetiology of psychosis or substance-induced psychosis, with no separate data provided, and (*c*) clinical outcome was not explicitly defined. Childhood was defined as age $\leqslant$18 years. UHR was defined as the presence of attenuated psychotic symptoms *OR* brief limited intermittent positive psychotic symptoms *OR* schizotypal personality disorder *OR* a family history of a psychotic disorder in a first-degree relative (full definition criteria can be found in Yung *et al.* 2004). FEP was defined as patients who were: making their first treatment contact for a psychotic disorder (schizophrenia-spectrum and affective psychoses) *OR* in their first admission for a psychotic disorder *OR* in their first episode of psychosis. Adversity included all forms of childhood abuse and neglect, parental death or separation, bullying by peers and being taken into care. Additional studies were identified by hand searching the bibliographies of each article found. Where the same study was reported in more than one publication, the dataset was only included once.

Only studies with sufficient statistical information for the computation of effects comparable to other reported studies were included. Each study was assessed using a quality assessment tool (see Supplementary material) adapted from Beards *et al.* (2013). A cut-off score of at least 11 out of 14 (>70%) was chosen to define the more 'methodologically robust' studies, based on criteria such as sample selection bias, measurement of exposure to childhood adversity, measurement of psychotic symptoms, and assessment of confounding.

Statistical analyses

All analyses were carried out using the meta-analysis commands of Stata v. 11 (StataCorp., 2009). We choose odds ratios (ORs) as the main outcome metric. When not reported in the primary studies, ORs and their associated standard errors were estimated from available descriptive statistics (i.e. frequencies) using standard computational techniques for dichotomous data. To examine the global association between adverse childhood events and persistence of psychotic symptoms, a meta-analysis was carried out on the effects extracted from studies providing a summary measure of exposure to childhood adversity. When this information was not available (i.e. in the absence of a

summary measure of childhood adversity or studies reporting multiple effects for the associations between adverse events and specific psychotic symptoms), reports were excluded to avoid bias stemming from the violation of statistical independence. Furthermore, all analyses were also stratified by population (clinical or general population) in order to assess whether findings differed across sample types. Standardized effect sizes were meta-analysed using random-effects models. Heterogeneity between studies was assessed with the Q test (Der Simonian & Laird, 1986). The I^2 statistic was calculated to express the proportion of variation between studies that was due to heterogeneity (Higgins *et al.* 2003). The results are displayed using a forest plot.

Further exploration of heterogeneity was carried out using meta-regression analyses for testing effects of the following potential moderator variables: population studied (a two-level factor: clinical *v.* general population), inclusion of adjusted or unadjusted effect sizes, year of publication, quality score, and length of follow-up. Egger's test of publication bias was used to assess whether there was a tendency for selective publication of studies based on the nature and direction of results (Egger *et al.* 1997). A significance level of $p<0.05$ was used for the random-effects model, homogeneity, publication bias and meta-regression analyses.

Results

The search yielded a total of 2824 studies (Fig. 1). On the basis of title and abstract, a total of 243 studies were considered potentially relevant and the full text of each was assessed manually. Of these, 223 did not satisfy one or more of the inclusion criteria and were excluded. A summary of the 20 eligible studies and their empirical findings relating to the association between childhood adversity and persistence of psychotic phenomena is provided in Table 1. Nine were studies of general population samples, three of UHR individuals, and eight of psychosis patient samples. A total of 13 studies scored above the cut-off of $\geqslant 11$ ($\geqslant 70\%$) and thus were considered to have a reasonable level of methodological quality.

Childhood adversity and persistence of PE

Among the available studies, childhood adversity tended to be associated with persistence of PE over time in general population samples, with ORs ranging from 1.8 to 3.26 (Wigman *et al.* 2011*a*, *b*; Konings *et al.* 2012). For instance, Wigman *et al.* (2011*a*, *b*) investigated patterns of the developmental course of PE at 2 and 6 years in a sample of female twins, aged 18–45 years, and a cohort of adolescents, aged 10–11 years at baseline, respectively. The authors identified four groups with distinct developmental trajectories of low, decreasing, increasing and persistent levels of PE. In both samples, exposure to childhood adversity significantly predicted persistent PE group membership with a dose-response effect. However, PE and childhood adversity were assessed using self-report questionnaires rather than gold standard interviews which may have adversely impacted on the quality of the data obtained and the sample of twins was restricted to women thus limiting generalizability.

Another study found that child rape predicted stability of PE over time, independently of cannabis use (Murphy *et al.* 2013). However, this result was not confirmed for sexual assault more broadly and other types of childhood adversity were not assessed. Additionally, Mackie *et al.* (2011) found that bullying victimization increased the risk of persistent PE by three times in a sample of adolescents assessed over a period of 18 months. Peer victimization predicted persistent class membership over and above all the other risk factors, such as depression, anxiety and substance use. Only one study included in this section did not show evidence of association between childhood adversity and course of psychotic symptoms. Escher *et al.* (2002) found that delusional ideation over a 3-year period was not significantly associated with higher levels of reported childhood adversity in adolescents who were hearing voices (hazard ratio 1.25, $p=0.100$). However, the sample included only 80 adolescents, some of the subjects were quite young at the time of assessment (age range 9–19), and baseline hallucinatory experiences could also have been driving the findings.

Childhood adversity and transition to psychotic disorder

A total of three studies investigating the association between childhood adversity and transition to psychosis in individuals at high risk for psychosis were included. A high-risk 3-year cohort study, following individuals with higher than average genetic risk for psychotic disorder (van Nierop *et al.* 2013), found that transition to psychosis was associated with childhood adversity [adjusted OR 34.4, 95% confidence interval (CI) 4.4–267.4] with an estimate of 86% of transitions in this type of population attributable to childhood trauma (van Nierop *et al.* 2013). However, only nine subjects had a transition to psychosis, with eight reporting early trauma, and no adjustment for baseline psychotic symptoms was made, which could have biased the results.

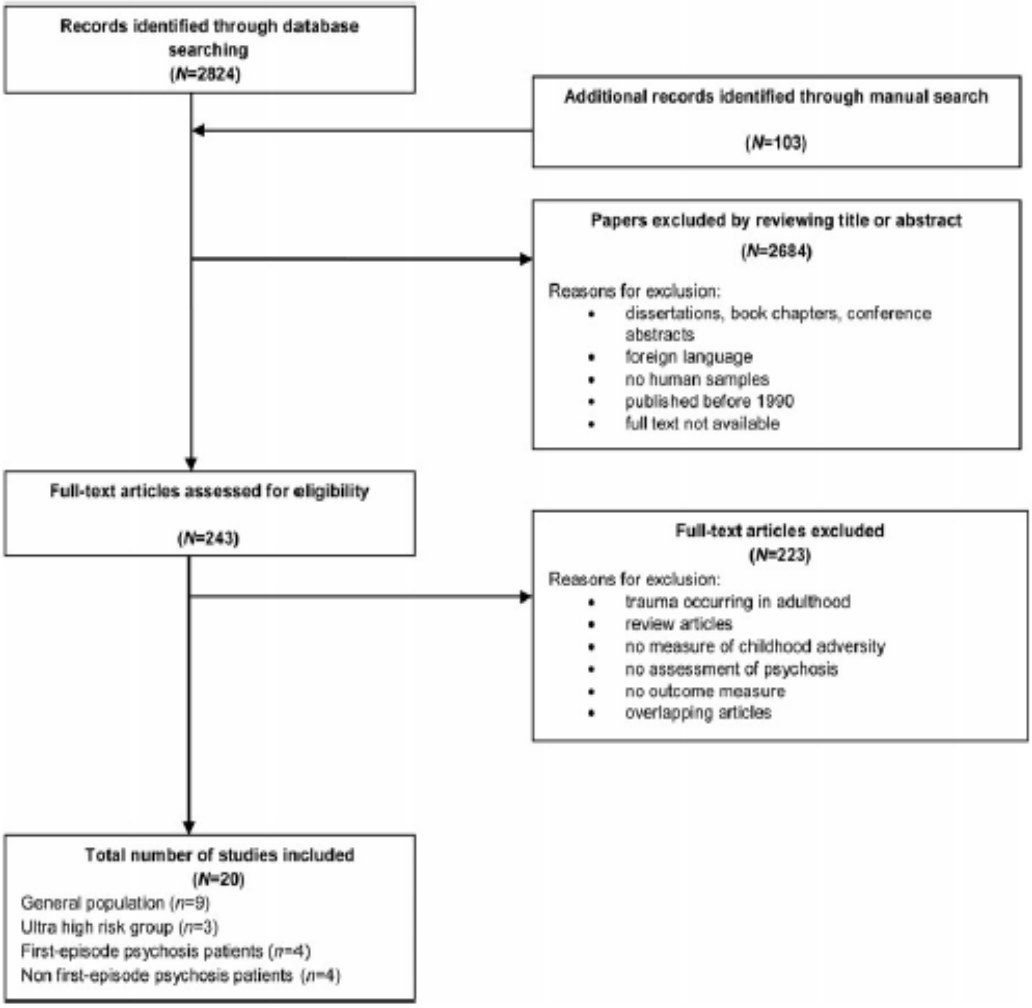

Fig. 1. Flow chart of published papers selected and excluded from the initial online database search to the publications included in the review.

Two studies conducted on individuals at UHR of psychosis, assessed the association between childhood adversity and transition to psychosis in a help-seeking clinical population with attenuated psychotic symptoms. Specifically, Bechdolf *et al.* (2010) reported that 36% of the UHR patients experienced sexual trauma and such experiences increased the chances of converting to psychotic disorder by almost three times (OR 2.96), compared to those UHR patients that did not report experiencing such adversity during childhood. However, the association fell short of statistical significance in the case of other types of childhood adversity, such as physical and emotional abuse and neglect (Bechdolf *et al.* 2010). Moreover, the relationship between trauma and onset of psychotic disorder may have been confounded by the early intervention programme provided to all participants, which might have reduced the rate of conversion to psychosis. These findings were replicated in a larger UHR cohort with a longer follow-up (Thompson *et al.* 2014), confirming a positive association between experience of childhood sexual abuse and psychosis transition, such that the higher the sexual abuse score the higher was the risk of transition to a psychotic disorder in the medium-to-long term. This was not the case for other types of trauma (physical or emotional abuse or neglect). Therefore, there is some evidence for a specific association between sexual trauma and transition to psychosis in this help-seeking population.

Childhood adversity and persistence of psychotic symptoms in patients with psychotic disorders

A total of eight studies were conducted on patients with a full-blown psychotic disorder. Four studies investigated the association between childhood

Table 1. *Studies included in the review which explore the association between childhood adversity and persistence of psychotic experiences or symptoms split into general population, ultra-high risk, first-episode and chronic psychosis patient samples*

Authors/study	N[a]	Follow-up period	Type of childhood adversity	Measure of childhood adversity	Outcome measure and definition	Main findings	Quality score
General population							
Escher *et al.* (2002) (The Netherlands)	At baseline: 80 At follow-up: 60	3 years	Death, illness, accidents, friends moving away, changing school, first menstruation, pregnancy, unanswered love, arguments, parental divorce, repeating school year	Structured interview	Positive psychotic symptoms (suspiciousness, unusual thought content, hallucinations) Maastricht Voices Interview for Children Extended Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962)	Childhood adversity influencing discontinuation of voices (HR 1.25; 95% CI 0.93–1.69, $p=0.1$)	10
Kelleher *et al.* (2013) Irish Center of the Saving and Empowering Young Lives in Europe (SEYLE) study (Ireland)	At baseline: 1112 At follow-up: 979 Prevalence of physical assault (n): 10% (111) Prevalence of bullying (n): 39% (409)	12 months	Physical assault and bullying	Participants were asked at baseline if they had been physically attacked in the past 12 months A series of yes-or-no questions were used to assess bullying	Hallucination and delusions Adolescent Psychotic Symptom Screener (Kelleher *et al.* 2011)	Physical assault predicted psychotic experiences at 3 and 12 months (OR 4.80, 95% CI 1.33–17.39; OR 6.19; 95% CI 1.64–23.30). Bullying reported at baseline predicted psychotic experiences at 3 and 12 months (OR 4.35, 95% CI 1.80–10.53; OR 3.40, 95% CI 1.35–8.55)	13
Konings *et al.* (2012) The Greek National Perinatal Study (Greece)	At baseline: 4675 At follow-up: 3500 Prevalence of maltreatment 'sometimes' (n): 58% (940); 'often' (n): 12% (196)	19 years	Physical punishment	Parental questionnaire	Lifetime psychotic experiences in the positive, negative and depressive symptom dimensions of psychosis in the general population. Community Assessment of Psychic Experiences (CAPE) (Konings *et al.* 2006)	Childhood maltreatment associated with psychosis outcome [adjusted B linear trend over three levels = 0.11, 95% CI 0.03–0.18, $p=0.006$]	13

Table 1 (*cont.*)

Authors/study	N[a]	Follow-up period	Type of childhood adversity	Measure of childhood adversity	Outcome measure and definition	Main findings	Quality score
The Netherlands Mental Health Survey and Incidence. Study (NEMESIS) (The Netherlands)	At baseline: 7076 At follow-up: 4842 Prevalence of moderate/severe maltreatment: 8.5%	3 years	Emotional, physical, psychological and sexual abuse	Semi-structured interview	Composite International Diagnostic Interview (CIDI version 1.1, computerized version)	Childhood maltreatment associated with psychosis outcome (OR 1.96, 95% CI 1.73–2.20, $p < 0.001$)	15
Mackie *et al.* (2011) (London, United Kingdom)	At baseline: 2148 At follow-up = 409	18 months	Bullying victimization	Four questions from the revised Olweus Bully/Victim Questionnaire (Olweus, 1996)	Hallucinatory experiences and delusional beliefs. Diagnostic Interview Schedule (Costello *et al.* 1982)	Bullying victimization associated with persistent psychotic experiences (OR 2.8, 95% CI 1.2–6.8, $p < 0.05$)	11
Murphy *et al.* (2013) National Comorbidity Survey-Replication (NCS-R)	At baseline: 9282 At follow-up: 2355 Prevalence of childhood rape (*n*): 5.8% (192) and childhood sexual assault (CSA): 8.3% (274)	10 years	Childhood rape and childhood sexual assault (CSA)	Posttraumatic Stress Disorder module of the modified version of the CIDI 3.0	Paranoia, delusions, hallucinations. Psychosis module (Section 27) of the CIDI 3.0	Childhood rape contributed to stability of psychotic symptoms ($B = 0.30$, S.E. = 0.04, $B = 0.16$; $p < 0.05$)	13
Rössler *et al.* (2014) The Zurich Study (Switzerland)	At baseline: 4547 At follow-up: 591 Total adversity score mean (S.D.) = 1.67 (1.68)	20 years	Parental neglect, conflicts among and with parents, father's mental illness, having been 'punished more severely than other children' and having been 'an unpopular mate'	SPIKE (Structured Psychopathological Interview and Rating of the Social Consequences of Psychological Disturbances for Epidemiology)	Paranoid ideation and psychoticism. Symptom Checklist 90-R (SCL90-R) (Derogatis, 1977)	Schizotypal signs significantly related to childhood adversity ($B = 0.019$)	12

Spauwen *et al.* (2006) The Early Developmental Stages of Psychopathology (EDSP) study (Germany)	At baseline: 3021 At follow-up: 2548 Prevalence of trauma (*n*): 19.5% (491)	42 months	Physical threat, serious accident, sexual abuse	Trauma module from the CIDI	Psychosis Proneness: thought interference, hallucinations and suspiciousness. Munich Composite International Diagnostic Interview (DIA–X/M–CIDI; Wittchen & Pfister, 1997), Self-report Symptom Check List-90 – Revised (SCL-90-R; Derogatis, 1983)	Trauma associated with persistence of psychotic symptoms (OR 2.60, 95% CI 1.66–4.09)	14
Wigman *et al.* (2011*a*) East Flanders Prospective Twin Survey (EFPTS) (Belgium)	At baseline: 621 At follow-up: 579	430 days	Physical, emotional, sexual abuse, physical and emotional neglect	Short version of the Childhood Trauma Questionnaire (CTQ; Bernstein *et al.* 1994; Arntz & Wessel, 1996)	Delusions, hallucinations, paranoid ideation and psychoticism; positive, negative and depressive dimensions of the subclinical psychosis phenotype in the general population. The Structured Clinical Interview for DSM-IV Axis I disorders SCID-I (First *et al.* 1998)	Persistent (expression of psychotic experiences) group was associated with childhood trauma (OR 3.26, 95% CI 1.77–6.00, $p < 0.0001$)	10
Wigman *et al.* (2011*b*) Tracking Adolescents Individual Lives Survey (TRAILS) (The Netherlands)	At baseline: 2230 At follow-up: 2230 Prevalence of severe trauma between 11–16 (*n*): 8% (157)	62.1 months	Victim of violence, gossip, bullying or sexual harassment	Self-report	Sub-threshold psychotic experiences Thought Problem subscale of the Youth Self-Report The Community Assessment of Psychic Experiences (CAPE; Stefanis *et al.* 2002) positive experiences subscale	Childhood trauma significantly predicted persistence of psychotic experiences (OR 2.18; CI 1.66–2.85, $p < 0.001$)	10
Ultra high-risk (UHR)							
Bechdolf *et al.* (2010) ORYGEN Youth Health (OYH) (Melbourn, Australia)	At baseline: 92 At follow-up: 92 Prevalence of at least one trauma (*n*): 69.6% (76)	615 days	Physical trauma/abuse; sexual trauma/abuse; emotional trauma/neglect; life-threatening accident; natural disaster; direct combat experience in war; witness	General Trauma Questionnaire (GTQ; Creamer *et al.* 2001)	Transition to psychosis Comprehensive Assessment of At-Risk Mental States (CAARMS; Young *et al.* 2005)	History of sexual abuse increased the chances of converting to psychotic disorder (OR 2.9, 95% CI 1.2–7.6, $p < 0.05$)	11

Table 1 (*cont.*)

Authors/study	N[a]	Follow-up period	Type of childhood adversity	Measure of childhood adversity	Outcome measure and definition	Main findings	Quality score
Thompson *et al.* (2014) Personal Assessment and Clinical Evaluation (PACE) study (Melbourne, Australia)	At baseline: 416 At follow-up: 233 Average total CTQ score: 47.8 (S.D.=18.4)	7.5 years	Physical abuse, sexual abuse, emotional abuse, physical neglect, emotional neglect	Childhood Trauma Questionnaire (CTQ; Bernstein *et al.* 2003)	Transition to psychotic disorder Comprehensive Assessment of At-Risk Mental States (CAARMS; Young *et al.* 2005) Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962)	Sexual abuse was related to transition to psychosis (HR 1.05, 95% CI 1.01–1.09, $p=0.023$)	12
van Nierop *et al.* (2013) GROUP study (The Netherlands and Belgium)	At baseline: 1057 At follow-up: 810 Prevalence of early trauma (*n*): 24% (255)	3 years	Emotional, physical and sexual abuse, emotional and physical neglect	Dutch version of the Childhood Trauma Questionnaire (CTQ; Bernstein *et al.* 1997)	Transition to psychotic disorder The Community Assessment of Psychic Experiences (CAPE; www.cape42.homestead.com)	Childhood trauma associated significantly with transition to psychosis (adj OR 34.4, 95% CI 4.42–267.4)	12
First-episode psychosis (FEP) patients							
Álvarez-Jiménez *et al.* (2011) (Australia)	At baseline: 413 At follow-up: 274 Prevalence of parental loss (*n*): 15% (41)	7.5 years	Parental loss	Information obtained from the patient, family members, members of the specialist treatment team or general practitioner and examination of psychiatric/research medical records	Number of psychotic episodes WHO Life Chart Schedule (LCS) (WHO, 1992)	Loss of one or both parents increased the risk of having more than one psychotic episode fourfold (adj OR 5.25, 95% CI 1.03–26.68, $p=0.045$)	11

Conus *et al.* (2010) (Australia)	At baseline: 658 At follow-up: 230 Separation of parents (42.1%, *n* = 277), physical abuse (26.0%, *n* = 171), sexual abuse (16.0%, *n* = 105). 34% reporting sexual or physical abuse (SPA)	18 months	Sexual and/or physical abuse (SPA)	Early Psychosis File Questionnaire (EPFQ; Conus *et al.* 2007)	Severity of illness Clinical Global Impressions-Severity of Illness Scale (CGI-S; Guy, 1976)	SPA was not related to either symptomatic (OR 0.88, 95% CI 0.75–1.05, *p* = 0.150) remission at discharge	13
Greenfield *et al.* (1994) (USA)	At baseline: 71 At follow-up: 38 Prevalence of physical abuse (*n* = 9, 23.7%); sexual abuse (*n* = 3, 7.9%), physical and sexual abuse (*n* = 8, 21.1%)	18 months	Childhood sexual and physical abuse	Life Experiences Questionnaire (LEQ; Bryer *et al.* 1987)	Psychotic symptoms Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962); Clinical Global Impression Scale (CGI; Guy, 1976)	No significant differences in recovery rates were observed between abused and non-abused subgroups	7
Uçok & Bickmaz (2007) (Turkey)	At baseline: 75 At follow-up: 57	6 months	Childhood sexual, physical, emotional abuse and physical and emotional neglect	Childhood Abuse Questionnaire (CAQ; Sar *et al.* 1999). Childhood Trauma Questionnaire's short version (CTQ; Bernstein and Fink, 1998)	Psychotic symptoms Brief Psychiatric Research Scale (BPRS; Ventura *et al.* 1986). Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984); Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983)	Significant association between emotional abuse and total score for positive symptoms (*r* = 0.278, *p* = 0.04), visual hallucinations (*r* = 0.289, *p* = 0.03), delusions of reference (*r* = 0.385, *p* = 0.005) and mind reading (*r* = 0.381, *p* = 0.006). Patients who reported childhood emotional neglect (CEN) had higher psychiatric symptoms (69.6, S.D. = 15.9 *v.* 60.3, S.D. = 13, *Z* = −2, *p* = 0.04), delusions of reference scores. Physical neglect was linked to the severity of visual and tactile hallucinations (*Z* = 2.1, *p* = 0.03)	9

Table 1 (*cont.*)

Authors/study	*N*[a]	Follow-up period	Type of childhood adversity	Measure of childhood adversity	Outcome measure and definition	Main findings	Quality score
Non FEP patients							
Davidson *et al.* (2009) Northern Irish study (Northern Ireland)	At baseline: 41 At follow-up: 31 Prevalence of childhood trauma (*n*): 55% (17)	18 months	Emotional, physical and sexual abuse, emotional and physical neglect	Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998)	Positive and negative psychotic symptoms. The revised Manchester Scale, KGVM (Krawiecka Goldberg Vaughan–Modified) Symptom Scale (Krawiecka *et al.* 1977) Version 6.2 (Lancashire, 1998)	No differences between the no childhood trauma ($n = 14$) and childhood trauma groups on KGVM score over 18 months ($F_{1,27} = 2.31$, $p > 0.05$)	9
Goff *et al.* (1991) Erich Lindemann Mental Health Center, Massachusetts General Hospital. (Massachusetts, USA)	At baseline: 72 At follow-up: 62 Prevalence of childhood abuse (*n*): 37.5% (27)	1 year	Physical and sexual abuse	Life Experiences Questionnaire (Bryer *et al.* 1987)	Delusions, hallucinations, and thought disorder. Structured Clinical Interview for DSMIII-R (SCID; Spitzer *et al.* 1987). Structured Clinical Interview for DSM-III R Dissociative Disorders (SCID-D; Steinberg *et al.* 1990). Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962)	Patients reporting childhood abuse relapsed more frequently than patients not reporting abuse histories (mean = 1.7, S.D.: 2.3, $p < 0.05$)	12
Lysaker *et al.* (2005) VA Medical Center (Indiana, USA)	At baseline: 65 At follow-up: 43 Prevalence of childhood abuse (*n*): 28% (18)	4 months	Sexual abuse	The Childhood Experiences Questionnaire (CEQ; Levitan *et al.* 1998)	Positive symptoms and emotional discomfort symptoms. The Positive and Negative Syndrome Scale (PANSS; Kay *et al.* 1987)	The abuse group had overall higher positive component scores ($F_{1,41} = 4.12$, $p < 0.05$). An interaction between group and time was noted at the trend level ($F_{7,41} = 1.92$, $p = 0.07$)	7

van Dam *et al.* (2014) GROUP study (The Netherlands and Belgium)	At baseline: 1119 At follow-up: 633 Prevalence of childhood adversity (*n*): 44% (336)	3 years	Emotional, physical and sexual abuse, emotional and physical neglect	Dutch version of the Childhood Trauma Questionnaire (CTQ; Bernstein *et al.* 2003; Thombs *et al.* 2009)	Positive and negative psychotic symptoms. The Positive and Negative Syndrome Scale (PANSS; Kay *et al.* 1987)	Total trauma associated with more severe positive and negative symptoms: Baseline Positive symptoms, mean (S.D.): Low trauma 1.65 (0.67) *v.* High trauma 2.01 (0.91); Follow-up, mean (S.D.): Low trauma 1.47 (0.59) *v.* High trauma 1.70 (0.69). Baseline Negative symptoms, mean (S.D.): Low trauma 1.81 (0.80) *v.* High trauma 2.01 (0.94); Follow-up, mean (S.D.): Low trauma 1.60 (0.64) *v.* High trauma 1.72 (0.79)	12

Adj., adjusted; CI, confidence interval; HR, hazard ratio; OR, odds ratio; S.D., standard deviation; S.E., standard error.
[a]Number of participants included in the study. For references cited in Table 1, see online Supplementary material.

adversity and course of psychotic symptoms in FEP samples with mixed findings. Álvarez-Jiménez *et al.* (2011) found that the loss of one or both parents was associated with a four-fold increased risk of having more than one psychotic episode over a 7.5-year follow-up period. However, two studies (Conus *et al.* 2010; Greenfield *et al.* 1994) observed no significant differences between sexually and/or physically abused and non-abused psychosis patients in terms of symptomatic remission (OR 0.88, $p = 0.150$) or recovery over 18 months following first admission. Similarly, Uçok & Bickmaz (2007), in their 6-month follow-up study, reported no correlation between sexual or physical abuse and severity of positive or negative symptoms but significant correlations for emotional abuse and emotional and physical neglect. Studies on FEP focused on different types of adversity and psychosis outcomes which makes it difficult to compare their results.

A total of four studies focused on non-FEP cases. In the study by Davidson *et al.* (2009), 55% of participants from community mental health services in Northern Ireland reported a history of childhood adversity. Although the authors reported no statistically significant differences between those with and without a history of childhood adversity in terms of the course of psychotic symptoms over time, patients who reported childhood adversity had higher positive and negative symptom scores at all the three assessments (baseline, 9 and 18 months) compared to patients who did not. Similarly, in the GROUP study sample (van Dam *et al.* 2014), individuals with childhood adversity reported higher levels of symptoms at both baseline and 3-year follow-up compared to individuals without such reports, indicating that heightened symptom levels were present over time. Interestingly, these results were consistent in unaffected siblings and controls, with those reporting trauma during childhood also having higher schizotypy levels at both baseline and follow-up. However, the association between trauma and developmental course of psychotic symptoms and schizotypy did not reach statistical significance. Similar findings come from shorter follow-up studies, with patients reporting physical or sexual abuse having higher levels of positive symptoms over 4 months and more frequent relapses over 1 year than patients not reporting abuse histories (Goff *et al.* 1991; Lysaker *et al.* 2005). However, the numbers of patients in these two studies was small (<100 in each study) and no other types of adversity were considered so the generalizability of these findings is limited.

Meta-analysis

Additionally, we carried out a meta-analysis of a subset of nine studies in which the ORs between adverse childhood events and persistence of psychotic symptoms had been reported (Fig. 2). Due to the low number of studies and heterogeneity of the samples of individuals at UHR of psychosis, this subgroup was excluded from the analyses. The meta-analysis for general population studies yielded a weighted OR of 1.76 (95% CI 1.19–2.32, $p < 0.001$), which suggests that individuals who reported childhood adversity were almost two times more likely to report persistence of PEs than those without reported adversity. However, there was significant heterogeneity between this subgroup of studies ($I^2 = 58\%$, $p = 0.049$).

Interestingly, the OR for the clinical samples (OR 1.55, 95% CI 0.32–2.77, $p = 0.007$) was similar to that for the general population studies (OR 1.76, 95% CI 1.19–2.32, $p < 0.001$), and indicated a significant association between childhood adversity and persistence of psychotic symptoms even after illness onset. Heterogeneity did not reach significant levels in this subgroup of clinical studies ($I^2 = 0\%$, $p = 0.407$) and there was no significant heterogeneity overall ($I^2 = 36.4\%$, $p = 0.114$). In the meta-regression analyses, there were no effects of population studied, inclusion of adjusted or unadjusted effect sizes, year of publication, quality score, or length of follow-up (results, not shown, are available from the authors).

Discussion

The goal of this review was to combine results from existing studies exploring the association between childhood adversity and course of psychotic symptoms, which is novel for the literature. We focused on trajectories of PE in the general population, transition to psychosis in individuals at UHR, and course of psychotic symptoms in clinical samples. There were two main findings: (*a*) the literature on childhood adversity and course of psychotic symptoms is surprisingly small (only 20 studies spread over 23 years); (*b*) most studies suggest that childhood adversity impacts on the course of both PE and clinically relevant psychotic symptoms, with our meta-analysis suggesting around a two-fold increased odds of persistence of psychotic phenomena in those reporting childhood adversity compared to those who did not. Therefore, the findings of this review could be seen to provide some support for aetiological continuity between subclinical and clinical psychosis phenotypes (van Os *et al.* 2009). Indeed previous studies have reported that individuals who persistently reported PE were more likely to report other risk factors for schizophrenia compared to individuals with low endorsement of PE (Thapar *et al.* 2012). However, in clinical samples there were inconsistent findings with some studies not confirming the effect of childhood adversity on symptom course

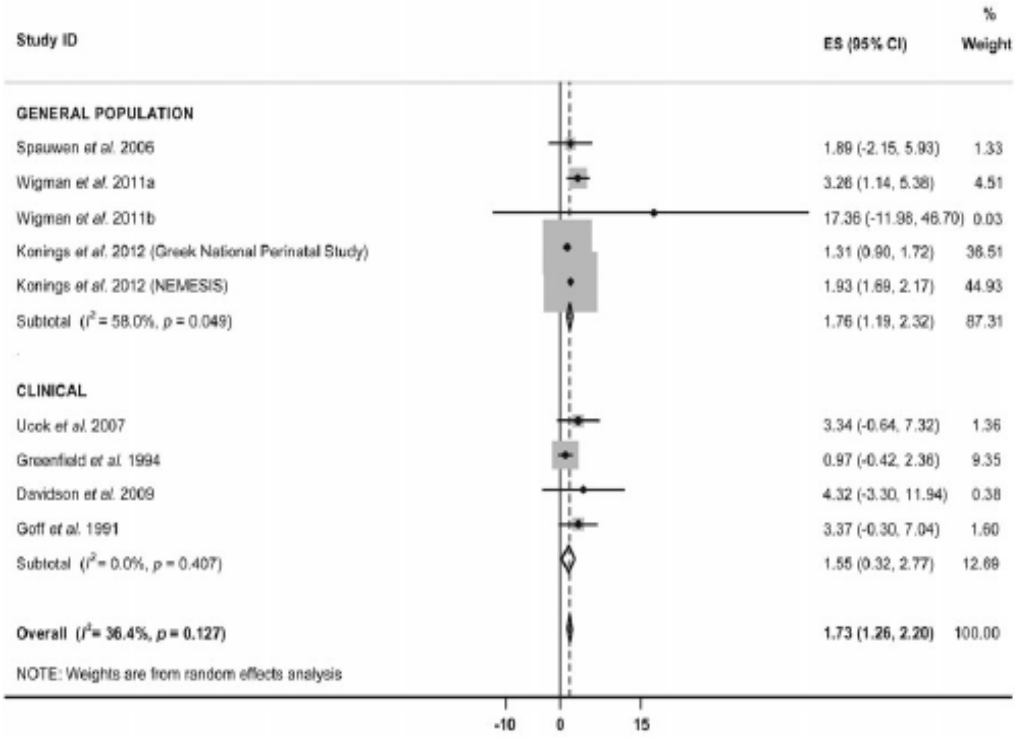

Fig. 2. Forest plot for the meta-analysis examining the overall association between childhood adversity and persistence of subclinical psychotic experiences and clinically relevant psychotic symptoms. CI, confidence interval; ES, effect sizes are displayed as odds ratios.

(e.g. Greenfield *et al.* 1994; Davidson *et al.* 2009; Conus *et al.* 2010). Moreover, very few studies have been published on conversion to psychotic disorder in relation to experience of adversity and thus it is still not possible to draw any firm conclusions in the UHR group due to the lack of findings.

Methodological issues

The findings of this review should be interpreted in the context of the strengths and limitations of the studies included. A major strength is that all 20 studies included used a prospective design. This design allows us to tentatively make causal inferences regarding the association between childhood adversity and course of psychotic symptoms compared to cross-sectional studies, at least in terms of the temporal ordering of the exposure and outcome. Another important strength of the studies in this review is that data on PE was available at two or more time-points, covering the transition period between childhood and adolescence, which is considered an important stage in the development of psychotic phenomena (Thapar *et al.* 2012). Data on clinical psychotic symptoms was also available at different time-points, allowing tentative inferences to be made concerning potential trajectories in the prodromal phase as well as after the illness onset. Furthermore, trajectory-based analyses are more robust to occasional misreporting or temporary fluctuations in a condition compared to data collected at a single time-point (Willett & Sayer, 1994; Wang & Bodner, 2007). Finally, the prevalence rate of childhood adversity, within the studies reviewed here, varied between 8% and 39% in the general population and between 8.5% and 69.6% in clinical samples, depending on the type of childhood adversity studied. This is similar to rates found in previous reviews of adversity and psychosis onset (Read *et al.* 2005; Varese *et al.* 2012).

However, there are a number of methodological limitations to the studies included in this review. A significant one is the variability in definitions and study parameters making comparisons between studies difficult and limiting the generalizability of the findings. There are currently no systematic methods of classifying adversity; so different criteria are employed for assessing the characteristics of adversity exposure (e.g. severity and frequency) making comparisons of findings between different studies or research groups very difficult (Cicchetti, 1994; Manly *et al.* 1994). Instruments to assess childhood adversity generally fall into two categories: checklist or semi-structured interview. Of the studies reviewed, nine used checklists, two used a checklist that was interviewer administered, and 9 used semi-structured interviews. Thus

differing rates of experiences may have been captured by the different assessment tools. Additionally, the majority of studies included in this review relied on retrospective self-reports of childhood adversity. Although self-report of childhood adversity has been criticized because of the susceptibility to memory deficiencies, it has been shown that reports of early adversity by psychosis patients appear reliable over time and between assessment methods (Fisher *et al.* 2011). The assessment of outcome variables was also not uniform across the studies and heterogeneity was significant for assessment of PE in general population studies. The heterogeneity of outcome definitions as well as the different types and severity of childhood adversity included reduce the comparability and sample size for each variable, limiting the validity and relevance of conclusions.

Moreover, causal interpretations in clinical studies are limited by the small number of first-episode and non-FEP samples available and by the lower methodological quality of clinical compared to non-clinical studies. It is clear that more methodologically robust studies based on clinical samples are needed, which utilize appropriate outcome measures and objective ratings of the impact of childhood adversity. Finally, adjustment for potential confounders was inconsistent. Where adjustments were made, the majority controlled for age, gender, and ethnicity, with some controlling for a wider range of factors, such as substance use or psychotic symptoms at baseline, and education. No study adjusted for adversity occurring in adulthood which has also been associated with the onset and course of psychosis (Beards *et al.* 2013).

Theoretical and clinical implications

If there is a continuum of psychosis, then it is likely that at least some of the environmental and genetic causes contributing to variation at the highest disorder level of the continuum also impact at lower levels. The psychosis proneness–persistence–impairment model, in fact, considers that some of the non-genetic risk factors associated with schizophrenia such as urbanicity, ethnic minority status, childhood adversity and cannabis use may also impact on the rate of PE (van Os *et al.* 2009). According to this model, developmental expression of PE is common and mostly transitory (Linscott & van Os, 2013). However, PE may become persistent through a mechanism of psychological and biological sensitization, depending on the degree of environmental risk the person is additionally exposed to. Persistence in turn might increase the probability of onset of impairment and need for care (Cougnard *et al.* 2007).

Furthermore, persistence of psychotic symptoms may be related to an underlying process of dopamine sensitization, associated with repeated exposure to environmental risk factors acting on a final common pathway (Collip *et al.* 2008; van Winkel *et al.* 2008; Howes & Murray, 2014). Exposure to adverse experiences early in life might alter the function of the hypothalamus–pituitary–adrenal (HPA) axis, potentially leading to atypical responsiveness of the HPA axis to later stressors, which in turn may predispose to psychiatric vulnerability in later life (Read *et al.* 2005; van Goozen & Fairchild, 2008; McCrory *et al.* 2011; Mondelli *et al.* 2011). Elevated cortisol levels, pronounced reductions in hippocampal volume, activation of dopaminergic circuits and the impact of pre- and post-natal factors in the aetiology of schizophrenia support the hypothesis of a link between childhood adversity, HPA activity, and psychosis (Walker & Diforio, 1997).

Cognitive and affective mechanisms might also be involved in the persistence of psychotic phenomena. Negative perceptions of the self, anxiety, and depression have been found to partially mediate associations between early adversity and emergence of PE (Fisher *et al.* 2013) in keeping with cognitive models of psychosis (Garety *et al.* 2007), though other psychological mechanisms are also likely to be involved (Bentall *et al.* 2014). Studies have also shown that cognitive factors and depression may be involved in the maintenance of psychotic symptoms over time (Vorontsova *et al.* 2013), though this has not been explored specifically in the context of adversity exposure. Therefore, there are several biological and psychological mechanisms, by which childhood adversity may not only increase risk for onset of PE and symptoms but also impact on the course of such phenomena, which merit further research attention.

Finally, it is possible that an association between childhood adversity and persistence of PE might go some way towards accounting for poorer outcomes of individuals with depression that have a history of childhood adversity. Childhood maltreatment has been associated with a more chronic course of depression (Brown *et al.* 2007) and a meta-analysis revealed that childhood maltreatment was associated with lack of response or remission during treatment for depression with psychological therapy, antidepressant medication, or combined treatment (Nanni *et al.* 2012). PE has been shown to confer a high risk for development of depression (Verdoux *et al.* 1999) and the presence of PE among individuals with depression has been linked to more severe depressive symptoms and worse treatment response (Wigman *et al.* 2012, 2014; van Os, 2014). Therefore, assuming a robust association could be found between childhood adversity

and persistence of PE, then it would be plausible to suggest that persistent PE might be mediating the association between childhood adversity and poorer outcome of depression. This is merely speculation and requires investigation. Moreover, it is unclear whether a history of childhood adversity would also impact on treatment outcomes in psychosis patients but this would be a useful avenue for future research in order to inform early intervention and prevention strategies.

Conclusions

This systematic review suggests that victims of childhood adversity may demonstrate a more persistent symptomatic course of clinical or subclinical psychosis compared to non-victims. However, it should be noted that much of the existing research is methodologically limited and this necessarily urges caution in drawing any firm inferences about the role of adverse childhood events in the course of psychotic disorder or PE. To date, only a few studies have focused on this issue and the broadness and the variety of outcome measures make it difficult to have a clear idea about the state of the art. Further research is warranted to develop a greater understanding of which individuals with psychosis are likely to have the poorest outcomes and whether this is associated with exposure to different forms of adversity as this would assist clinicians in targeting interventions at those patients with the highest risk of a poor prognosis. Specifically, it is clear that more methodologically robust investigations are needed into the association between childhood adversity and course of psychotic phenomena based on general population, high-risk and clinical samples, which utilize more objective ratings of a range of early adverse experiences, include well-defined outcome measures obtained prospectively over multiple time-points and take into account relevant confounders.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S0033291715000574.

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Declaration of Interest

Robin M. Murray is an editor of this journal.

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APPENDIX III - Trotta et al. (2015a) supplementary material

Supplementary Material (1) Search Terms

1. Psychosis-related search terms ("psychosis"; "Schizophrenia"; "psychotic"; "Hallucination"; "Delusion"; "Prodrom*"; "prodrom* symptom*"; "ultra-high risk"; "high risk"; "attenuated psycho*"; "subclinical symptom*"; "psychosis continuum"; "attenuated symptom*"; "subclinical psychosis"; "at-risk-mental-state"; "psychotic symptom*"; "psychotic experience*"; "paranoia"; "psychotic-like")

2. Childhood adversity related search terms: ("child* trauma"; "child* advers*"; "child* maltreat*"; "child* abuse"; "child* neglect" OR "child* stressful life event*"; "separat*"; "child* loss"; "peer victim*"; "negligent treatment"; "bull*"; "death"; "violen*"; "institution*"; "exploitat*"; "authority care"; "punishment"; "injur*"; "divorce"; "abandon"; "foster"; "adopt")

3. Course of symptoms related terms: ("outcome"; "course"; "hospital*"; "chronic"; "relapse"; "recover*"; "impair*"; "treatment response"; "follow-up"; "admission"; "remission"; "admitted"; "remitted"; "detention"; "sectioned"; "detained"; "episodic"; "continuous"; "sever*"; "treatment resistant"; "recurrent"; "persisten*"; "transition").

Supplementary Material (2) Quality Reporting Scale

Items	Quality score*
A. Selection Bias	
(1) Are the individuals selected to participate in the study likely to be representative of the target population?	
- There was a non-random selection process or the sampling method was not reported.	0
- The sample was made up of either incident cases or randomly sampled controls, or there were no control subjects.	1
- In case-control/cohort studies, the sample was made up of incident cases and randomly sampled controls. In general population studies, the entire sample was randomly selected.	2
(2) What percentage of selected individuals agreed to participate?	
- Less than 50% of participants, or not reported or not applicable.	0
- 50-69% of participants.	1
- 70-100% of participants.	2
(3) What is the sample size?	
- Less than 50 subjects in each group	0
- At least 50 subjects in each group	1
- At least 100 cases and controls or sample size calculation indicating adequate statistical power.	2
(4) What percentage of selected individuals was retained in the study?	
- Less than 50% of participants, or not reported or not applicable.	0
- 50-69% of participants.	1
- 70-100% of participants.	2
B. Measurement of exposure – Childhood adversity	
(5) What was the quality of the childhood adversity measurement tool?	

- Self-report checklist 0
- Interviewer administered checklist 1
- Semi-structured interview 2

(6) Did the measure assess different types of traumas?

- No distinction was made between different types of trauma, or not reported. 0
- There was an assessment of different types of trauma but they were not explored separately in the analysis. 1
- There was an assessment of different types of trauma and they were analysed separately. 2

C. Measurement of outcome – Psychotic symptoms

(7) How were psychotic symptoms measured?

- Clinician-only diagnosis 0
- Structured assessment by trained research worker, or self-report measure for psychotic-like experiences 1
- Structured assessment by clinician 2

D. Confounding

(8) Was there an assessment of confounding and consideration in the analysis?

- No adjustment for confounders 0
- Adjustment for basic demographics e.g. age, gender, ethnicity, socioeconomic status 1
- Potential confounders were measured and adjusted for in the analysis e.g. adjustment of basic demographics and other risk factors such as urbanicity, drug/alcohol use, social support 2

*Scores of 11 or more (70% or over) were considered to indicate methodological quality.

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APPENDIX IV – Trotta et al. (2015b) paper

Trotta, A., Murray, R.M., David A.S., Kolliakou A., O'Connor, J., Di Forti M., Dazzan, P., Mondelli, V., Morgan, C., Fisher, H.L. (2015). Impact of Different Childhood Adversities on One-Year Outcomes of Psychotic Disorder in the GAP study. *Schiz Bull*, doi:10.1093/schbul/sbv131.

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Impact of Different Childhood Adversities on 1-year Outcomes of Psychotic Disorder in the Genetics and Psychosis study

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While the role of childhood adversity in increasing the risk of psychosis has been extensively investigated, it is not clear what the impact of early adverse experiences is on the outcomes of psychotic disorders. Therefore, we investigated associations between childhood adversity and 1-year outcomes in 285 first-presentation psychosis patients. Exposure to childhood adversity prior to 17 years of age was assessed using the Childhood Experience of Care and Abuse Questionnaire. Data on illness course, symptom remission, length of psychiatric hospitalization, compliance with medication, employment, and relationship status were extracted from clinical records for the year following first contact with mental health services for psychosis. Seventy-one percent of patients reported exposure to at least 1 type of childhood adversity (physical abuse, sexual abuse, parental separation, parental death, disrupted family arrangements, or being taken into care). No robust associations were found between childhood adversity and illness course or remission. However, childhood physical abuse was associated with almost 3-fold increased odds of not being in a relationship at 1-year follow-up compared to patients who did not report such adverse experiences. There was also evidence of a significant association between parental separation in childhood and longer admissions to psychiatric wards during 1-year follow-up and 2-fold increased odds of noncompliance with medication compared to those not separated from their parents. Therefore, our findings suggest that there may be some specificity in the impact of childhood adversity on service use and social functioning among psychosis patients over the first year following presentation to mental health services.

Key Words: first episode/illness course/psychosis/trauma/psychotic symptoms/service use

Introduction

There is a wealth of evidence suggestive of an association between childhood adversity (eg, physical and sexual abuse, neglect, death of or separation from a parent) and psychosis,[1–3] reported from both general population[4–10] and clinical studies.[11–14] However, little is known about the effect of experiences of adversity during childhood on the course or outcomes of psychosis. There have been reports that childhood adversity is associated with persistence of psychotic symptoms,[15] higher number of suicide attempts,[16] poor medication adherence,[17] and increased risk of readmission and relapse.[18] In terms of social and vocational functioning, some previous studies have reported that childhood adversity is linked with a higher rate of unemployment[19] and increased service costs,[20] and these detrimental outcomes are maintained over time.[21]

However, other studies have not confirmed the effect of childhood adversity on clinical and social course of psychosis.[22,23] The heterogeneity of the samples employed, the variety of outcome measures utilized, the reliance on self-rated assessments of adversity, and the tendency to focus on only 1 or 2 types of childhood adversity make it difficult to draw firm conclusions.

This study aimed to determine the impact of different types of childhood adversity on 1-year outcome across 3 domains (clinical, social, and service use) in a catchment-based sample of individuals presenting to mental health services for the first time with psychotic disorder.

childhood adversity predicts an unfavorable course of depression[24] and bipolar disorder,[16,25,26] it was hypothesized that individuals with psychosis who reported exposure to any type of childhood adversity would have a worse outcome 1 year after first presentation when compared with those who did not report such adverse experiences.

Methods

Participants

The sample was drawn from patients who participated in the Genetics and Psychosis Biomedical Research Centre (GAP-BRC) study from the Lambeth, Southwark, Lewisham, and Croydon adult in-patient and out-patients units of the South London and Maudsley Mental Health NHS Foundation Trust (SLAM). Inclusion criteria for cases were: age 18–65 years, presenting to psychiatric services for the first time with a psychotic disorder (codes F20–29 and F30–33 from the International Classification of Diseases [ICD-10])[27] and resident within tightly defined catchment areas in Southeast London, UK. Exclusion criteria were: organic psychosis, intelligence quotient (IQ) under 70, previous contact with services for psychosis, and transient psychotic symptoms resulting from acute intoxication. ICD-10 diagnoses were determined using data from the Schedules for Clinical Assessment in Neuropsychiatry (SCAN).[28] Ethical permission was obtained from the SLAM and the Institute of Psychiatry Research Ethics Committee.

Baseline Assessment

Baseline assessment and diagnostic interviews were performed by qualified psychologists and psychiatrists, subject to comprehensive training, and achievement of good interrater reliability. A range of sociodemographic information was obtained including age at interview, gender, current level of education, and self-ascribed ethnicity using the UK 2001 census categories. Duration of untreated psychosis (DUP) was defined as the period in weeks from the onset of psychosis to first contact with mental health services and it was calculated based on full clinical notes (with some informant interviews) of each patient using the Nottingham Onset Schedule-DUP.[29] The Global Assessment of Functioning (GAF)[30] scale was used to rate both severity of symptoms and disability. We assigned 2 separate ratings on the GAF based on dimensions of psychiatric symptoms (GAF-symptoms) and psychological, social, and occupational functioning (GAF-disability).

Childhood Adversity

The Childhood Experience of Care and Abuse Questionnaire (CECA.Q)[31] was employed at baseline to retrospectively elicit information from participants Physical abuse by the main mother and father figures (usually but not necessarily the biological parents), sexual abuse by an individual at least 5 years older than the recipient, separation from a parent for at least 6 months, death of a parent, taken into institutional care, and number of family arrangements, all prior to 17 years of age, were assessed. Every childhood experience section of the CECA.Q begins with screening questions and then positive responses are followed up with more detailed questions. The questionnaire was read out to all participants to improve the accuracy of the fixed category responses obtained. This questionnaire has been shown to have good internal consistency,[32] satisfactory levels of test-retest reliability over 7 years in a similar psychosis sample,[33] and reasonable concurrent validity with existing measures.[31–33]

One-Year Follow-up

The 1-year follow-up period was taken as the date of first contact with SLAM mental health services for psychosis to the date exactly 1 year later using the clinical records held on the SLAM electronic Patient Journey System (ePJS). All of the following measures were completed by a researcher retrospectively from electronic mental health records.

Follow-up Assessment and Definition of Outcomes

Information on course of illness (recovery, relapse episodes, continuous illness), remission from psychotic symptoms, relationship status, livelihood/occupation, compliance with medications, and number of days in hospital were collected with the Follow-up Psychiatric and Personal History Schedule (FU-PPHS).[34] The FU-PPHS, previously used in World Health Organization multicenter studies of the incidence and outcome of schizophrenia[35] and in previous studies of pathways to care,[36] has shown good validity and reliability.[35] Interrater reliability was established between 3 qualified psychologists on 10 training cases. Ratings of the presence or absence of symptoms were made on the basis of clear and definite information in the clinical records inserted by mental health professionals involved in patient care. Cohen's κ values indicated robust agreement among the 3 raters (range: 0.583–1.000, $P < .05$). Efforts were made to maintain interrater reliability across the entire follow-up, including careful calibration and standardization procedures and regular, in-depth review of a sample of assessments. Raters were blind to diagnostic information from previous baseline assessments.

Relapse was defined as the emergence of positive, negative, or disorganized symptoms following a period of remission of at least 30 days. Similarly, "remission" was also operationally defined as the absence of such symptoms for at least 30 days. Noncompliance with

medications was defined as: "lapses of 3 or more days more than once" or "not taking any prescribed medication." The total number of days spent in institutions included in-patient treatment in a psychiatric hospital ward to which the patient had been admitted because of a psychiatric disorder. Relationship status was defined as married or in a steady relationship at follow-up vs being single, divorced, or widowed at follow-up. Employment status was defined as being employed or involved in a study program in the last 30 days of follow-up vs being unemployed or not studying at follow-up. Student status was defined as being a full-time student at secondary school, technical or occupational college, or University.

GAF[30] scales were also completed from clinical records for the 7 days prior to the 1-year anniversary of first contact with mental health services for psychosis. Three researchers involved in rating the GAF via notes completed intensive reliability checks (intraclass correlation range: 0.974–1.000, all *P*'s < .001). The same raters were involved in the GAF and FU-PPHS record-based assessments to improve reliability.

Statistical Analysis

The guidelines published by Bifulco et al[31] were employed to create dichotomous variables for all the CECA.Q subscales. A composite variable was also computed to summarize how many of the different adversities had been experienced by each individual. This "total adversity" score involved summing the dichotomous CECA.Q subscale scores (range 0–6) and then recoding the total into an ordinal scale of 0 (none), 1 (single adverse experience), and 2 (multiple adverse experiences).

The total number of days spent in an institution for psychosis throughout the year following the first contact with mental health services was counted up (range 0–365 d). As the number of admission days was nonnormally distributed, with skewness of 1.71 (SE = 0.16) and kurtosis of 3.42 (SE = 0.32), the number of days that patients spent on a psychiatric ward was dichotomized at the median into less than 49 days vs 49 days or more.

Binary logistic regressions were used to analyze the relationship between each form of adversity and dichotomous follow-up variables (symptomatic remission, length of hospital admission, compliance with medications, relationship and employment status). Ordered logistic regressions and linear regressions were used for ordinal (illness course) and continuous normally distributed follow-up outcome variables (GAF-symptoms and GAF-disability scores at 1 year), respectively. All analyses were conducted using STATA release 11 (Stata-Corp).

Results

Prevalence of Childhood Adversity

Information on childhood adversity was available for 285 first-presentation psychosis patients. Exposure to at least 1 type of childhood adversity was found in 203 patients (71.2%), with 82 (28.8%) reporting multiple exposures. The most frequently occurring adverse childhood events were separation from parents (56.5%, *n* = 160), followed by physical abuse (22.8%, *n* = 65), disrupted family arrangements (3 or more arrangements; 20.7%, *n* = 56), and sexual abuse (14.4%, *n* = 41). Very few participants in this sample reported parental loss (11.7%, *n* = 33) or being taken into care during childhood (4.9%, *n* = 14). We have previously shown that all types of childhood adversity, except for sexual abuse, occurred more often among psychosis cases than unaffected controls.[11] Patients reporting childhood adversity had a lower level of education ($P < .001$), were more often of non-White ethnicity ($P < .001$), and had lower GAF-disability scores at baseline ($P = .033$) compared with patients who did not (see table 1). These variables were controlled for in the final adjusted model, where appropriate.

Follow-up Attrition Rate

At follow-up, of the 285 patients initially identified, 3 had died, 11 had left the country, 12 were discharged to a general practitioner (*n* = 6) or other mental health services (*n* = 6), and 22 were excluded on the basis of insufficient information available on ePJS. A total of 237 psychosis cases were active in ePJS at point of follow-up, giving a completion rate of 83.2%.

When patients with follow-up information available were compared with those without, there was a trend for difference in terms of gender ($\chi^2 = 2.584$, $P = .145$), but no evidence of systematic differences by age ($t = -0.247$, $P = .805$), ethnicity ($\chi^2 = 10.673$, $P = .470$), educational attainment ($\chi^2 = 5.584$, $P = .235$), baseline relationship status ($\chi^2 = 0.349$, $P = .693$), employment status ($\chi^2 = 0.004$, $P = 1.000$), or GAF-disability score ($t = -0.828$, $P = .409$). Similarly, patients with follow-up data did not differ in terms of clinical functioning at baseline (DUP $t = 1.146$, $P = .253$; GAF-symptom score $t = -0.724$; 0.470) or diagnosis ($\chi^2 = 1.104$, $P = .622$) from those without data. Additionally, there was no evidence that those who were not traceable were more likely to report a history of parental separation ($\chi^2 = 1.005$, $P = .341$), parental loss ($\chi^2 = 0.540$, $P = .621$), physical abuse ($\chi^2 = 2.217$, $P = .186$), sexual abuse ($\chi^2 = 1.717$, $P = .260$), institutional care ($\chi^2 = 0.069$, $P = 1.000$), or disrupted family arrangements ($\chi^2 = 0.197$, $P = .693$).

Childhood Adversity and Clinical Course of Psychosis

Over the first year of contact with mental health services, a total of 123 (55.1%) patients had no relapse episodes of psychotic symptoms following their initial episode. There was no evidence of associations between each type of childhood adversity with course of psychosis over the 1-year follow-up period (table 2).

Table 1. Baseline Sociodemographic and Clinical Characteristics of First-Presentation Psychosis Patients

Demographic and Clinical Characteristics	Total (N = 285) n (%)	Any Childhood Adversity: Yes (N = 203) n (%)	Any Childhood Adversity: No (N = 82) n (%)	χ^2	df	P
Gender				1.44	1	.285
Men	172 (60.4)	127 (62.6)	45 (54.9)			
Women	113 (39.6)	76 (37.4)	37 (45.1)			
Ethnicity				**36.28**	**5**	**< .001**
White British	72 (25.3)	39 (19.2)	33 (40.2)			
Black Caribbean	56 (19.6)	52 (25.6)	4 (4.9)			
Black African	65 (22.8)	50 (24.6)	15 (18.3)			
White other	30 (10.5)	21 (10.3)	9 (11.0)			
Asian (all)	24 (8.4)	10 (4.9)	14 (17.1)			
Other	38 (13.3)	31 (15.3)	7 (8.5)			
Level of education				**20.43**	**4**	**< .001**
No qualifications	48 (17.6)	40 (20.7)	8 (10.1)			
GCSE/O level	64 (23.5)	47 (24.4)	17 (21.5)			
A level	40 (14.7)	25 (13.0)	15 (19.0)			
Vocational/college	66 (24.3)	54 (28.0)	12 (15.2)			
University or professional qualifications	54 (19.9)	27 (14.0)	27 (34.2)			
Age (y)				t = 0.934	282	.351
Mean (SD)	28.9 (9.3)	28.6 (8.8)	29.7 (10.2)			
Duration of untreated psychosis (wk)				t = −0.773	173	.440
Mean (SD)	6.8 (11.0)	7.3 (11.6)	5.9 (9.8)			
GAF-symptoms score				t = 1.80	139	.073
Mean (SD)	46.9 (18.8)	44.9 (18.7)	51.4 (21.7)			
GAF-disability score				**t = 2.16**	**138**	**.033**
Mean (SD)	55.7 (16.9)	53.7 (15.6)	60.3 (18.9)			

Note: Figures in bold indicate P <.05. Any childhood adversity refers to reported exposure prior to 17 y of age to any of the following: separation from a parent, parental death, physical abuse, sexual abuse, being taken into care, or having more than 2 family arrangements. *df*, Degrees of freedom; GAF, Global Assessment of Functioning scale; GCSE, General Certificate of Secondary Education.

A total of 155 patients (67.1%) had a period of at least 30 days without psychotic symptoms during the first year of contact with mental health services. However, more than half the sample (55%, n = 138) reported moderate or severe symptoms 1 year after their first presentation to services (GAF-symptoms < 61). No evidence of associations were found between childhood adversity and either remission from psychotic symptoms (table 2) or for GAF-symptom scores at 1-year follow-up (table 3), except for parental loss which was strongly associated with lower symptom levels at 1 year (P = .003) and the association remained significant when a Bonferroni correction for multiple testing was applied (P = .05/8 = .006). There was no robust evidence of a dose-response effect for exposure to multiple adverse experiences on clinical course of psychosis, symptomatic remission, or global clinical functioning over 1-year follow-up in this sample.

Childhood Adversity and Social Outcomes of Psychosis

Table 4 presents the associations between types of childhood adversity and 1-year social outcomes. After adjustment for relationship status at baseline, reported exposure to physical abuse was associated with not being in a relationship at follow-up (P = .035), with almost a 3-fold increase in odds compared to patients who did not report this type of adversity (OR = 2.82). No associations were evident for the other adversities. A total of 169 (75.1%) patients of the overall sample were unemployed or not studying at 1 year. There was no evidence of associations with unemployment status at 1-year follow-up for psychosis cases reporting a history of childhood adversity compared to those who did not and no evidence of a dose-response effect for repeated adversity exposure.

In terms of overall social functioning at 1 year, a total of 169 (67.3%) patients showed moderate or severe disability 1 year after first presentation to services (GAF-disability < 61). There was no evidence of associations with GAF-disability scores for most types of adversity (table 3), though there was evidence that experiences of parental loss were associated with better functioning at 1 year (P < .001), also after correcting for multiple testing (P = .05/8 = .006). However, the CI were very wide (11.03–34.28) indicating that this result should be interpreted cautiously. No robust evidence of a cumulative effect for repeated adverse experiences on social outcomes of psychosis over 1-year follow-up was found.

Childhood Adversity and Service Use

The median length of admission over the first year since presentation to services was 48.5 days spent in

Table 2. Adjusted Associations Between Different Types of Childhood Adversity and 1-y Clinical Outcomes

	Course of Illness					Remission			
Type of Childhood Adversity	No Relapses, Complete or Nearly Complete Recovery *n* (%)	One or More Relapses *n* (%)	Continuous Illness *n* (%)	OR[a] (95% CI)	*P*	Yes *n* (%)	No *n* (%)	OR[a] (95% CI)	*P*
Parental separation									
No (*n* = 97)	56 (57.7)	21 (21.6)	20 (20.6)	-	-	66 (67.3)	32 (32.6)	-	-
Yes (*n* = 128)	68 (53.1)	29 (22.7)	31 (24.2)	1.25 (0.56–2.78)	.583	88 (67.2)	33 (32.8)	0.99 (0.42–2.33)	.982
Parental loss									
No (*n* = 200)	108 (54.0)	48 (24.0)	44 (22.0)	—	—	136 (67.3)	66 (32.7)	—	—
Yes (*n* = 24)	15 (62.5)	2 (8.3)	7 (29.2)	0.39 (0.10–1.58)	.187	17 (65.4)	9 (34.6)	1.84 (0.49–6.77)	.361
Physical abuse									
No (*n* = 176)	101 (57.4)	38 (21.6)	37 (21.0)	—	—	119 (67.6)	57 (32.4)	—	—
Yes (*n* = 51)	24 (47.7)	12 (23.5)	15 (29.4)	1.02 (0.36–2.86)	.973	36 (65.4)	19 (34.5)	1.00 (0.35–2.90)	.998
Sexual abuse									
No (*n* = 193)	105 (54.4)	43 (22.3)	45 (23.3)	—	—	131 (66.8)	65 (33.2)	—	—
Yes (*n* = 34)	20 (58.8)	7 (20.6)	7 (20.6)	1.06 (0.33–3.39)	.918	24 (68.6)	11 (31.4)	0.87 (0.26–2.92)	.819
Institutional care									
No (*n* = 216)	116 (53.70)	49 (22.69)	51 (23.61)	—	—	146 (66.4)	74 (33.6)	—	—
Yes (*n* = 11)	9 (81.82)	1 (9.09)	1 (9.09)	0.43 (0.04–4.43)	.473	9 (81.8)	2 (18.2)	2.50 (0.25–25.06)	.437
Family arrangements									
Up to 2 (*n* = 173)	98 (56.65)	35 (20.23)	40 (23.12)	—	—	116 (66.7)	58 (33.3)	—	—
3 or more (*n* = 46)	23 (50.00)	12 (26.09)	11 (23.91)	0.74 (0.27–2.02)	.558	31 (64.6)	17 (35.4)	1.92 (0.62–5.94)	.256
Total adversity									
0 (*n* = 65)	39 (60.0)	16 (24.6)	10 (15.4)	—	—	44 (67.7)	21 (32.3)	—	—
1 (*n* = 92)	46 (50.0)	20 (21.7)	26 (28.3)	1.09 (0.45–2.65)	.847	61 (65.6)	32 (34.4)	1.53 (0.60–4.04)	.390
2 or more (*n* = 70)	40 (57.1)	14 (20.0)	16 (22.9)	0.77 (0.27–2.20)	.632	50 (68.5)	23 (32.5)	1.51 (0.50–4.57)	.468

[a]Adjusted for duration of untreated psychosis and baseline Global Assessment of Functioning symptoms score.

hospital (interquartile range 21–102 days) and 64.1% of the sample (*n* = 132) was compliant with prescribed medications at 1-year follow-up. Results of the association between childhood adversity and length of hospitalization and medication compliance are shown in table 5. There was evidence of an association between parental separation in childhood and a longer admission to a psychiatric ward during 1-year follow-up, with cases reporting such adversity being approximately twice as likely to have longer hospital stays compared to those without such a history ($P = .012$). The association with length of hospitalization was stronger for participants who reported multiple (OR = 2.18, 95% CI: 1.11–4.29, $P = .023$) than single (OR = 1.57, 95% CI: 0.83–2.97, $P = .164$) adverse childhood experiences. A score test for trend provided evidence for a linear trend ($z = 2.27$, $P = .023$), indicating a dose-response effect on length of hospitalization for repeated adverse experiences.

Evidence of a 2-fold increased odds of noncompliance with medications was found amongst those patients who reported childhood exposure to parental separation or disrupted family arrangements, though the latter association fell just short of statistical significance ($P = .051$). The association with compliance with medication at 1 year was similar for psychosis patients who reported single (OR = 2.81) and multiple (OR = 2.22) adverse childhood experiences.

Discussion

To our knowledge, this is the first study systematically exploring the impact of different types of childhood adversity on 3 outcome domains over a 1-year period in first-presentation psychosis patients. Despite a high prevalence of childhood adversity in this sample (71%), compared to geographically matched controls (49%) reported in a previous study,[11] we found no robust evidence that

Table 3. Adjusted Associations Between Different Types of Childhood Adversity and Overall Clinical and Social Functioning at 1-y Follow-up

Type of Childhood Adversity	GAF Symptoms Mean (SD)	B[a] (95% CI)	P	GAF Disability Mean (SD)	B[b] (95% CI)	P
Parental separation						
No (*n* = 93)	59.3 (18.63)	—	—	54.7 (19.49)	—	—
Yes (*n* = 119)	58.0 (20.63)	−7.14 (−15.49 to 1.20)	.092	55.3 (19.71)	−1.12 (−9.48 to 7.25)	.791
Parental loss						
No (*n* = 187)	58.0 (19.17)	—	—	54.4 (18.82)	—	—
Yes (*n* = 24)	60.2 (24.22)	**18.72** (6.60–30.84)	**.003**	59.6 (24.15)	**22.64** (11.03–34.28)	**<.001**
Physical abuse						
No (*n* = 164)	58.7 (19.36)	—	—	55.3 (19.56)	—	—
Yes (*n* = 50)	57.7 (28.94)	−1.98 (−12.47 to 8.51)	.708	54.4 (19.50)	−0.46 (−11.04 to 10.12)	.931
Sexual abuse						
No (*n* = 181)	58.4 (19.84)	—	—	55.3 (19.38)	—	—
Yes (*n* = 33)	58.8 (19.19)	−0.81 (−12.84 to 11.21)	.893	54.1 (20.46)	−3.41 (−15.10 to 8.27)	.563
Institutional care						
No (*n* = 204)	58.1 (19.68)	—	—	54.5 (19.41)	—	—
Yes (*n* = 10)	67.0 (18.89)	10.83 (−9.28 to 30.95)	.288	67.3 (18.35)	12.42 (−7.33 to 32.17)	.215
Family arrangements						
Up to 2 (*n* = 162)	59.0 (19.71)	—	—	54.93 (19.48)	—	—
3 or more (*n* = 43)	55.8 (20.52)	1.30 (−9.68 to 12.29)	.814	56.42 (20.47)	3.63 (−7.21 to 14.46)	.508
Total adversity						
0 (*n* = 62)	59.6 (17.72)	—	—	55.4 (19.7)	—	—
1 (*n* = 85)	57.5 (19.80)	−2.31 (−12.02 to 7.38)	.636	53.5 (18.0)	0.41 (−9.42 to 10.23)	.935
2 or more (*n* = 67)	58.8 (21.40)	2.71 (−8.49 to 13.91)	.632	56.8 (21.3)	6.67 (−4.33 to 17.68)	.231

Note: *B*, regression coefficient. Figures in bold indicate $P < .05$.
[a]Adjusted for duration of untreated psychosis and baseline Global Assessment of Functioning (GAF) symptom score.
[b]Adjusted for duration of untreated psychosis and baseline Global Assessment of Functioning (GAF) disability score.

a history of adversity impacted on course of psychotic illness during the first year after presentation to services. This is inconsistent with previous findings that demonstrated associations between exposure to childhood abuse (sexual, physical, emotional)[16,18] or parental loss[36,37] and a more chronic course of illness.

However, in line with a previous study conducted on first-episode psychosis patients, in which childhood abuse was not associated with lack of symptomatic remission at follow-up,[22] in the current study experiences of childhood adversity were not associated with lack of remission from psychotic symptoms in the 1-year follow-up period. There were also no differences between patients who reported most types of childhood adversity and those who did not report any childhood adversity in severity of symptoms at 1-year follow-up. The exception was for death of a parent before 17 years of age which was significantly associated with slightly less severe symptomatology at follow-up. Previous studies found an association between childhood abuse and more severe psychotic symptoms,[38,39] though they were conducted on small samples (<100 patients) followed up to 6 months, and this makes comparison with the current study difficult.

In terms of social outcomes, psychosis patients reporting experiences of physical abuse in childhood were almost 3 times more likely to be single at follow-up compared to those patients that did not report this type of adversity, while no association was shown at baseline between the 2 subgroups (OR = 1.40, $P = .360$). Previous studies have shown that patients with psychosis who reported a history of childhood abuse had higher rates of avoidance and discomfort with closeness,[40] and fewer of the psychological resources necessary for sustaining intimacy[41] compared to those without such a history. Similar findings come from studies on adults with post-traumatic stress disorder[42,43] that highlight an association between emotional distress and significant deficits in metacognition, namely the capacity of thinking about the thoughts and feelings of others.[44] Attachment theory also suggests that early disruption of attachment in childhood can cause

Table 4. Adjusted Associations Between Different Types of Childhood Adversity and 1-y Social Outcomes

Type of Childhood Adversity	Relationship Status				Employment Status			
	In a Relationship *n* (%)	Not in a Relationship *n* (%)	OR[a] (95% CI)	*P*	Employed *n* (%)	Not Employed *n* (%)	OR[b] (95% CI)	*P*
Parental separation								
No (*n* = 100)	33 (33.0)	67 (67.0)	—	—	27 (28.1)	69 (71.9)	-	-
Yes (*n* = 131)	34 (25.9)	97 (74.1)	1.16 (0.56–2.39)	.655	28 (22.0)	99 (78.0)	0.97 (0.48–1.96)	.932
Parental loss								
No (*n* = 207)	61 (29.5)	146 (70.5)	—	—	47 (23.4)	154 (76.6)	-	-
Yes (*n* = 23)	7 (30.4)	16 (69.6)	0.84 (0.27–2.63)	.765	8 (38.1)	13 (61.9)	0.52 (1.17–1.53)	.234
Physical abuse								
No (*n* = 179)	56 (31.3)	123 (68.7)	—	—	47 (26.6)	130 (73.4)	-	-
Yes (*n* = 54)	12 (22.2)	42 (77.8)	**2.82** (1.07–7.43)	**.035**	9 (18.7)	39 (81.3)	1.67 (0.67–4.17)	.273
Sexual abuse								
No (*n* = 199)	61 (30.7)	138 (69.3)	—	—	48 (25.1)	143 (74.9)	-	-
Yes (*n* = 34)	7 (20.6)	27 (79.4)	1.33 (0.48–3.74)	.583	8 (23.5)	26 (76.5)	0.96 (0.37–2.49)	.928
Institutional care								
No (*n* = 222)	66 (29.7)	156 (70.3)	—	—	52 (24.3)	162 (75.7)	-	-
Yes (*n* = 11)	2 (18.2)	9 (81.8)	1.79 (0.30–10.44)	.521	4 (36.4)	7 (63.6)	0.47 (0.11–1.99)	.304
Family arrangements								
Up to 2 (*n* = 179)	52 (29.1)	127 (70.9)	—	—	48 (27.6)	126 (72.4)	-	-
3 or more (*n* = 45)	15 (33.3)	30 (66.7)	0.85 (0.34–2.07)	.716	8 (19.0)	34 (81.0)	1.54 (0.60–3.92)	.365
Total adversity								
0 (*n* = 67)	22 (32.8)	45 (67.2)	—	—	20 (30.3)	46 (69.7)	-	-
1 (*n* = 96)	30 (31.2)	66 (68.8)	0.93 (0.40–2.13)	.861	21 (22.6)	72 (77.4)	0.84 (0.36–1.95)	.687
2 or more (*n* = 70)	16 (22.9)	54 (77.1)	1.56 (0.61–3.99)	.348	15 (22.7)	51 (77.3)	1.14 (0.47–2.75)	.774

Note: Figures in bold indicate $P < .05$.
[a]Adjusted for baseline relationship status
[b]Adjusted for baseline employment status.

difficulties in source monitoring, emotion recognition, and the ability to form coherent representations of oneself and others,[45–47] thus impairing the ability to initiate and maintain satisfying relationships in adulthood.[48,49]

No strong evidence for associations were found between types of childhood adversity and unemployment status at 1-year follow-up, though the ORs for physical abuse (OR = 1.67) and disrupted family arrangements (OR = 1.54) were suggestive of slightly higher proportions unemployed amongst these patients. Consistent with the current study, Conus et al[22] found that a history of sexual and/or physical abuse amongst first-episode psychosis patients was not associated with unemployment. However, previous research has highlighted the link between childhood adversity and a higher rate of unemployment in patients with severe mental disorders over longer follow-up periods.[18,19]

In the current study, we also did not find robust associations between a history of childhood adversity and the global measure of social and vocational functioning at 1-year follow-up, with the exception of parental loss which, paradoxically, was associated with slightly better functioning. The negative results are largely in keeping with previous findings that first-episode psychosis patients exposed to sexual or physical abuse during childhood showed no differences in terms of functional outcome compared to nonexposed patients at 18-month follow-up.[22] However, studies conducted in samples of chronic patients reported deficits in functioning in those reporting a history of adversity during childhood.[19,21,41,50,51] This raises the possibility that the impact of some forms of childhood adversity may only be evident over longer follow-up periods or in those with more chronic forms of psychosis.

Finally, though, we did find that psychosis patients reporting a history of parental separation were more likely to spend longer on psychiatric wards and be noncompliant with medications 1 year after first contact

Table 5. Adjusted Associations Between Different Types of Childhood Adversity and 1-y Service Use

	Length of Hospital Admission				Compliance With Medications			
Type of Childhood Adversity	Less Than 49 d *n* (%)	49 d or More *n* (%)	OR[a] (95% CI)	*P*	Compliant *n* (%)	Not Compliant *n* (%)	OR[b] (95% CI)	*P*
Parental separation								
No (*n* = 98)	59 (60.2)	39 (39.8)	—	—	61 (70.9)	25 (29.1)	—	—
Yes (*n* = 136)	59 (43.4)	77 (56.6)	**2.45** (1.06–5.66)	**.035**	69 (58.5)	49 (41.5)	**2.34** (1.11–4.92)	**.026**
Parental loss								
No (*n* = 207)	103 (49.7)	104 (50.2)	—	—	117 (64.6)	64 (35.4)	—	—
Yes (*n* = 26)	13 (50.0)	13 (50.0)	0.67 (0.19–2.35)	.536	12 (54.5)	10 (45.5)	1.18 (0.39–3.57)	.766
Physical abuse								
No (*n* = 178)	91 (51.1)	87 (48.8)	—	—	102 (64.5)	57 (35.8)	—	—
Yes (*n* = 58)	27 (46.5)	31 (53.4)	1.42 (0.51–4.00)	.504	30 (63.8)	17 (36.2)	1.23 (0.50–3.01)	.659
Sexual abuse								
No (*n* = 199)	99 (49.7)	100 (50.2)	—	—	118 (65.9)	61 (34.1)	—	—
Yes (*n* = 37)	19 (51.3)	18 (48.6)	0.74 (0.22–2.46)	.619	14 (51.9)	13 (48.1)	1.50 (0.51–4.35)	.458
Institutional care								
No (*n* = 224)	110 (49.1)	114 (50.9)	—	—	106 (66.7)	53 (33.3)	—	—
Yes (*n* = 12)	8 (66.7)	4 (33.3)	0.64 (0.10–4.16)	.637	21 (51.2)	20 (48.8)	1.25 (1.20–7.83)	.813
Family arrangements								
Up to 2 (*n* = 178)	89 (50.0)	89 (50.0)	—	—	106 (66.7)	53 (33.3)	—	—
3 or more (*n* = 48)	21 (43.7)	27 (56.2)	1.60 (0.55–4.71)	.390	21 (51.2)	20 (48.8)	2.67 (1.00–7.17)	.051
Total adversity								
0 (*n* = 66)	40 (60.6)	26 (39.4)	—	—	43 (74.1)	15 (25.9)	—	—
1 (*n* = 95)	47 (49.5)	48 (50.5)	2.36 (0.89–6.20)	.081	51 (58.6)	36 (41.4)	**2.81** (1.15–6.84)	**.023**
2 or more (*n* = 75)	31 (41.3)	44 (58.7)	2.28 (0.77–6.79)	.139	38 (62.3)	23 (37.7)	2.22 (0.82–6.05)	.117

Note: Figures in bold indicate $P < .05$.
[a]Adjusted for duration of untreated psychosis and baseline Global Assessment of Functioning symptom score.
[b]Adjusted for duration of untreated psychosis and baseline compliance with medication.

with psychiatric services compared to those who did not report this childhood experience. Previous first-episode psychosis studies have also found significant associations between childhood adversity and longer stays in hospital,[21] a higher number of admissions to hospital,[18] and poor medication adherence.[17] Moreover, individuals with traumatic childhood experiences have shown difficulties in seeking help and in maintaining relationships,[52,53] especially with authority figures such as health professionals.[17,54] Because of such difficulties, it might be challenging for mental health professionals to establish a good therapeutic alliance with patients with a history of parental separation[55] and this, in turn, might prolong the time spent on a psychiatric ward and/or reduce compliance with treatments, including medication.

Limitations

There are several limitations to this study. First, we assessed childhood adversity using retrospective self-report. Although several studies have shown some bias in retrospective reports,[56] such bias is considered insufficiently great to invalidate retrospective case-control studies of childhood experiences.[57] Moreover, previous studies have demonstrated that the effect of childhood adversity on psychosis remains significant regardless of study design[2] and histories of childhood adversity obtained by psychosis patients appear reliable over time and unaffected by current symptoms.[33,58] Moreover, we utilized the CECA.Q to assess adversity which contains additional questions to obtain concrete details of the reported experiences and severity is determined by the researcher based on this additional information, thus reducing the subjectivity inherent in self-reports. We also attempted to enhance the validity of the self-reported experiences by scoring the severity of the responses in a standardized manner (see www.cecainterview.com), and using conservative cutoffs to ensure only severe adversity was considered in analyses. All of these factors increase the likelihood of an individual accurately remembering past adverse

experiences.[51] Given the low prevalence rate of psychotic disorders in the general population (approximately 3%),[59] it would be very difficult to attempt to collect data on childhood adversity prospectively in a birth cohort as the sample size required to obtain a sufficient number of clinical cases would be too large to be cost-effective.

Second, although this was a fairly large first-presentation sample, the low prevalence of some forms of adversity is likely to have reduced our power to detect statistically significant associations with psychosis outcomes. This is indicated by reasonably wide CIs particularly for associations with being taken into care and parental loss. Therefore, our findings should be treated with appropriate caution and further research is required in larger epidemiological samples. It is also possible that the lack of impact on outcomes found for some forms of adversity was due to the length of delay between reported exposure to childhood adversity and subsequent onset and presentation to services for psychosis. However, the majority of our sample (81%) were aged 35 years or younger at presentation to services and only 2 cases were aged 60 or above, suggesting that for most patients this delay was not too long. Moreover, prospective studies have reported that effects of childhood adversity on mental and physical health outcomes persist over several decades.[60–62]

Our study failed to support a dose-response effect of childhood adversity on 1-year outcomes. These results might be an artifact of the approach we adopted to conceptualize and measure this dose-response effect. Schilling et al[63] showed that the severity of childhood adversity experienced is more important in terms of later mental health outcomes than a simple cumulative adversity score. Similarly, Clausen and Crittenden[64] argued that single instances of certain types of abuse (eg, physical or sexual) may be traumatic enough to produce detrimental effects while other adverse experiences may require repeated exposure to cause harm to the child. Therefore, if time had permitted, it would have been preferable to conduct a more in-depth interview, such as the full CECA interview,[65] with participants to obtain more detailed information about their experiences and potentially improve the accuracy of reporting.[57] This would allow investigation of the timing of exposure as well as relationship to perpetrators of childhood maltreatment and revictimization. Additionally, only specific types of adversity occurring during childhood were investigated in this study. Other forms of childhood adversity, such as bullying and exposure to domestic violence[66,67] and other stressful life events in adulthood[68] which have also been previously associated with psychosis, might demonstrate stronger associations with psychosis outcomes and confound the relationships found in the current study.

Another important limitation of this study is represented by selection and information bias arising from loss to follow-up and missing or inaccurate data. In an attempt to minimize attrition, the whereabouts or status of over 90% of the cohort was determined. Comparing those with and without some information available on course and outcome, there was no strong evidence of systematic bias. Although this does not entirely rule out selection bias, it does suggest attrition is unlikely to have seriously affected these findings. Nevertheless, the outcome data were obtained from clinical records rather than face-to-face interviews, thus limiting the type of outcomes that could be assessed. It is possible that periods of remission or information on overall clinical functioning were overestimated or underestimated as patients do not always disclose symptoms to clinicians and clinicians do not always accurately record what patients say. Additionally, many different healthcare professionals were involved in patient care, so the measurement of outcomes throughout the database would probably be less accurate and consistent than that achieved with a prospective cohort study design.[60] However, clinical ratings were made by consensus after careful consideration of all available information and all efforts were made to rate the presence or absence of symptoms on the basis of clear and definite information. Bebbington et al[30] also showed good reliability and validity of assessing remission and relapse in psychosis using case-notes.

Finally, duration of follow-up was relatively short, and it is possible that impact of trauma on outcome may become manifest only later and that 1-year follow-up may be accounted for by preexisting prognostic factors. Accordingly, the association between childhood adversities and clinical and social outcomes over 12 months has been corrected for the influence of several known baseline prognostic indicators, including DUP. Nonetheless, longer-term follow-up studies are required.

Clinical Implications

Given the high prevalence of childhood adversities reported by first-presentation psychosis cases in this sample, routine assessment of adversity history and psychotherapies focused on adverse childhood experiences should be considered by services providing treatment to psychosis patients. Moreover, as shown in this study, without considering past exposure to (at least some) adverse experiences, the efforts to engage and treat psychosis patients may be unsuccessful.[71] More research in this domain is therefore warranted, not only in order to better understand the mechanisms involved and direction of causality between adversity and its potential consequences but also to target psychological interventions to this complex issue.

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APPENDIX V – Trotta et al. (2015c) paper

Trotta, A., Di Forti, M., Iyegbe, C., Green, P., Dazzan, P., Mondelli, V., Morgan, D., Murray R.M., Fisher, H.L. (2015). Familial risk and childhood adversity interplay in the onset of psychosis. *BJPsych Open*, *1*, 6–13.

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Familial risk and childhood adversity interplay in the onset of psychosis

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Background
The association between childhood adversity and psychosis in adulthood is well established. However, genetic factors might confound or moderate this association.

Aims
Using a catchment-based case–control sample, we explored the main effects of, and interplay between, childhood adversity and family psychiatric history on the onset of psychosis.

Method
Childhood adversity (parental separation and death, physical and sexual abuse) was assessed retrospectively in 224 individuals with a first presentation of psychosis and 256 community controls from South London, UK. Occurrence of psychotic and affective disorders in first-degree relatives was ascertained with the Family Interview for Genetic Studies (FIGS).

Results
Parental history of psychosis did not confound the association between childhood adversity and psychotic disorder. There was no evidence that childhood adversity and familial liability combined synergistically to increase odds of psychosis beyond the effect of each individually.

Conclusions
Our results do not support the hypothesis that family psychiatric history amplifies the effect of childhood adversity on odds of psychosis.

Declaration of interest
None.

Childhood adversity has been shown to be associated with early psychotic symptoms,[1–3] with transition to clinical psychosis in individuals at ultra-high risk (UHR),[4] as well as with the onset of a full-blown psychotic disorder.[5–7] Furthermore, associations are usually stronger with increasing frequency and severity of the trauma experienced,[8] indicating a key role for this environmental factor in the development of psychosis. However, genetic vulnerabilities have been repeatedly shown to be involved in the aetiology of psychosis.[9] Studies have estimated the heritability of schizophrenia to be around 60%,[10] and concordance for schizophrenia in monozygotic twins is around 50%.[11] Moreover, having one or more biological parents with a history of psychosis has been associated with a greater risk of exposure to stressful life events and adverse experiences during childhood[12,13] and also with the development of psychotic symptoms and disorders.[14,15] This suggests that a 'passive' type of gene–environment correlation (rGE)[16] might be operating such that parents provide their children with both an adverse upbringing and a genetic vulnerability to developing psychosis. This implies that parents' genetic make-up may be confounding the childhood adversity–psychosis associations observed in previous studies.

It is also possible that genetic factors moderate the association between childhood adversity and psychosis (a gene–environment interaction, G × E),[16] potentially by influencing how an individual reacts biologically and/or psychologically following exposure to adversity which may set them off on the path to psychosis.[17] A number of studies have examined rGE and G × E using indirect measures of genetic risk, such as being a relative, a twin or adopted-away offspring of a person with schizophrenia.[18–20] The advantage of using familial liability to psychosis as a proxy for genetic risk is that it may capture a greater proportion of genetic load, including gene–gene interactions, in contrast to studies using direct molecular genetic measures that tend to incorporate only a small contribution to genetic variation in the form of single-nucleotide polymorphisms (SNPs).[21] Moreover, despite the advent of polygenic risk scores, which combine multiple SNPs and thus increase the amount of genetic variation accounted for, these may not provide any additional mechanistic clues over and above measures of family psychiatric history because they aggregate information across thousands of SNPs, thus making it difficult to disentangle which combinations of SNPs are driving the interaction.[22] It is important to note though that a history of psychosis and other psychiatric disorders in first-degree relatives is only a proxy for genetic risk and may also reflect some aspects of the environment in which individuals are brought up,[17] though this component is likely to be fairly small.[10] Therefore, at present there is no ideal measure of genetic risk to employ in exploring rGE and G × E for psychosis and thus triangulation of evidence obtained from different measures across multiple studies is likely to be the best overall strategy. Here we focus on trying to broaden the evidence base in relation to familial liability to psychosis.

Despite several studies previously investigating interactions between genetic liability and childhood adversity in the onset of psychosis, those involving familial liability as a measure of proxy genetic risk have been restricted to general population samples.[1,14,23–26] Only one study has investigated the interplay between childhood adversity and familial risk for mental health problems in a first-episode psychosis sample,[27] but this focused solely on one form of adversity, namely maternal physical abuse. In light of this, the aim of the present study was to extend existing research by investigating, for the first time, the interplay between various forms of childhood adversity and family psychiatric history in the onset of psychotic disorders. We sought to test two hypotheses: (a) individuals with a parental history of psychosis or affective disorders would have a greater

prevalence of both psychotic disorders and childhood adversity than those without this proxy genetic vulnerability; and (b) childhood adversity would combine synergistically (on an additive scale) with familial liability to increase the odds of psychotic disorder.

Method

Participants

The sample was drawn from patients who participated in the Genes and Psychosis (GAP) study from Lambeth, Southwark and Croydon adult in-patient units of the South London & Maudsley (SLAM) Mental Health National Health Service (NHS) Foundation Trust, UK. Inclusion criteria for patients were: age 16-65 years, presenting to psychiatric services for the first time with a psychotic disorder (codes F20-29 and F30-33 from the International Classification of Diseases (ICD-10)),[28] and resident within tightly defined catchment areas in south-east London, UK. Exclusion criteria were: organic psychosis; IQ < 50; previous contact with services for psychosis; and transient psychotic symptoms resulting from acute intoxication (ICD-10).[28] ICD-10 diagnoses were determined using data from the Schedules for Clinical Assessment in Neuropsychiatry (SCAN).[29]

Control participants were aged 16–65 years and recruited from the local population living in the area served by the Trust, by means of internet and newspaper advertisements, and distribution of leaflets at train stations, shops and job centres. Efforts were made to obtain a control sample that was representative of the general population in age, gender, ethnicity, educational qualifications and employment status. The Psychosis Screening Questionnaire (PSQ)[30] was administered to all potential control group participants; individuals were excluded if they met criteria for a psychotic disorder.

Measures

A range of sociodemographic information was obtained including age at interview, gender, current level of education and self-ascribed ethnicity (using the UK 2001 census categories) during face-to-face interviews using the Medical Research Council Socio-demographic Schedule.[31]

Childhood adversity

The Childhood Experience of Care and Abuse Questionnaire (CECA-Q)[32] was employed to retrospectively elicit information from participants concerning a range of adverse childhood experiences before the age of 17 years. For this analysis, physical abuse by the main mother and father figures (usually but not necessarily the biological parents), sexual abuse by any adult or an individual at least 5 years older than the recipient, separation from a parent for at least 6 months and death of a parent were included. Full details of the questionnaire are provided in Bifulco *et al*.[32] The CECA-Q has been shown to have good internal consistency,[33] satisfactory levels of test–retest reliability over 7 years in a psychosis sample[34] and reasonable concurrent validity with existing measures.[32–34] The CECA-Q elicits concrete examples of adverse experiences, and severity of the responses is scored in a standardised manner to enhance validity of the self-reported experiences.[32] Every childhood experience section of the CECA-Q begins with screening questions and then positive responses are followed up with more detailed questions. This questionnaire was read out to all participants to improve the accuracy of the fixed category responses obtained. The physical and sexual abuse variables were dichotomised into severe and non-severe categories using the most conservative published cut-off points.[32]

Family history of mental illness

The Family Interview for Genetic Studies (FIGS; https://www.nimhgenetics.org/interviews/figs) was used to obtain information about the participant's family history of mental health problems. This interview begins with a brief construction of a pedigree diagram for the participant's first-degree relatives and a series of screening questions to elicit information about possible mental health problems in these relatives. Positive responses to any of these are followed up with more specific questions to obtain symptom and treatment information for each potentially affected relative. Only three of these supplementary sections were chosen for this study, namely depression, mania and psychosis. For patients, this interview was supplemented by information retrieved from clinical records. To maximise genetic risk, only information on first-degree relatives (participant's biological mother and father, full siblings and children) was used. The FIGS consensus diagnoses were divided into several familial risk variables. First, a 'family mental illness' variable referred to the presence (1) or absence (0) of current or past psychosis, mania or depression in at least one first-degree relative. A 'family psychosis' variable denoted the presence (1) or absence (0) of a current or previous diagnosis of psychosis in at least one first-degree relative. A 'parental mental illness' variable was also created that indicated the presence (1) or absence (0) of a current or previous diagnosis of psychosis, mania or depression in at least one biological parent. Similarly, a variable for 'parental psychosis' was created that denoted the presence (1) or absence (0) of current or past psychosis in at least one biological parent.

Ethics

Ethical permission was obtained from the SLAM and the Institute of Psychiatry Research Ethics Committee. All participants provided written consent after reading a detailed information sheet.

Statistical analysis

All analyses were performed using Stata version 11.1 (StataCorp, College Station, TX, USA). First, main effects of each type of childhood adversity and (general and psychotic) family mental illness on psychosis caseness were assessed using a series of logistic regressions. Second, we tested whether differences in an individual's proxy genetic liability might drive differential environmental exposure. Specifically, the passive type of rGE was explored using binary logistic regression analysis to estimate odds ratios (ORs) of the associations between history of parental mental illness or parental psychosis and (a) psychotic disorder in the participants, and (b) each subtype of childhood adversity. If familial liability is associated with both disorder and adversity, then this indicates the possibility of a passive rGE (albeit a 'proxy gene' by environment correlation). The possibility that parental psychopathology may attenuate the association between childhood adversity and psychosis was also addressed by rerunning the association between childhood adversity and psychotic disorder with parental history of psychosis added as a confounder.

Next, we examined whether there was evidence that childhood adversity combined synergistically with each type of familial liability by testing for interaction on an additive scale using interaction contrast ratios (ICRs).[35,36] This approach uses ORs to estimate the relative excess risk due to interaction. Biological synergism (the odds of psychosis among individuals with both risk factors being greater than the sum of the independent effects of each risk factor) can be better estimated from additive statistical interaction than

multiplicative statistical interaction.[37,38] As the numbers of cases and controls with a family history of psychosis were very small, interaction analyses were only conducted for family and parental history of mental illness. *Post hoc* estimations of power and sample size were estimated using the 'sampsi' command in Stata 11. All analyses were controlled for gender (male or female), age at interview (16-64 years), ethnicity (White British, Black Caribbean, Black African, Asian [all], Mixed or Other) and level of education (no qualification, school-leaving qualifications, A-levels/vocational/college or university/professional qualifications).

Results

Information on family history of mental illness was available on 224 of the 285 patients and 250 of the 256 controls with a completed CECA-Q. The patients with and without FIGS data did not differ in terms of gender ($\chi^2 = 0.003$, $P = 1.000$), age ($t = 0.587$, $P = 0.558$) or diagnosis ($\chi^2 = 0.184$, $P = 1.000$). The basic demographic data by case and control status for those included in the analyses are presented in Table 1.

More than half of the patients were male (60.4%) and from Black or other minority ethnic groups (BME; 74.7%). The majority of the controls were also male (53.5%) and from BME groups (60.1%). Mean age at interview was around 29 years both for patients and controls. As expected, patients were significantly more likely to be from a BME group ($P < 0.001$), and have none or only school-leaving qualifications ($P < 0.001$) compared with controls. There was no significant difference in gender ($P = 0.065$) or age ($P = 0.733$) between patients and controls. These demographic factors were all controlled for in the analysis, either because they differed between patients and controls or because they have previously been shown to be associated with adversity exposure and psychosis. A total of 17 patients (6% of the overall sample) were found to have an IQ of 70 or below which is considered be the cut-off for mild intellectual impairment.[39] These individuals were sufficiently cognitively able to complete the assessments and thus were retained in the sample. Unfortunately, IQ data were not available on a large enough number of participants to be included as a confounder.

Association between childhood adversity and psychotic disorder

Table 2 presents the prevalence of each type of childhood adversity for psychosis patients and controls along with the ORs of the associations with case status. All types of childhood adversity, except for sexual abuse, occurred more often among psychosis patients than unaffected controls. Following adjustment for demographic factors, only the associations between parental separation and psychosis remained statistically significant, with sexual abuse ($P = 0.05$) and parental loss ($P = 0.06$) approaching significance. These results confirm the previously demonstrated association between childhood adversity and psychosis.

Association between familial liability and psychotic disorder

Table 3 presents the prevalence of each type of familial liability for psychosis patients and unaffected controls along with the ORs of the associations with case status. All types of familial risk were significantly associated with psychosis in probands. Psychotic disorders were around four times more common in first-degree relatives of patients than controls, while more broadly defined mental illness (psychosis, depression or mania) was almost twice as common. This indicates that familial liability could be considered as a proxy genetic risk factor for psychosis, though it could also indicate the negative environmental effects of living with a first-degree relative who has a serious mental disorder. In both cases, familial liability might play a role in the previously demonstrated association between childhood adversity and psychosis.

Proxy rGE for parental psychopathology and childhood adversity

In order to investigate the presence of a passive rGE, we tested whether parental psychopathology was also associated with childhood adversity in this sample. Therefore, the reported prevalence of parental mental illness and psychosis by exposure to childhood adversity for patients and controls is presented separately in Table 4. Parental psychopathology was not associated with greater exposure to any type of childhood adversity among patients in this sample.

Table 1 Basic demographic characteristics of psychosis patients and unaffected controls

Demographic variable	Patients ($n = 285$) n (%)	Controls ($n = 256$) n (%)	χ^2	d.f.	P
Gender			2.57	1	0.065
Male	172 (60.4)	137 (53.5)			
Female	113 (39.6)	119 (46.5)			
Ethnicity			32.60	5	<0.001
White British	72 (25.3)	102 (39.9)			
Black Caribbean	56 (19.6)	39 (15.2)			
Black African	65 (22.9)	32 (12.5)			
White other	30 (10.5)	50 (19.5)			
Asian (all)	24 (8.4)	16 (6.3)			
Other	38 (13.3)	17 (6.6)			
Level of education			76.73	4	<0.001
No qualifications	48 (17.6)	7 (3.0)			
School leaving qualifications	64 (23.5)	23 (10.0)			
A-levels/college level qualifications	40 (14.7)	53 (22.9)			
Vocational qualifications	66 (24.3)	37 (16.0)			
University or professional qualifications	54 (19.9)	111 (48.1)			
Age in years			$t = 0.342$	536	0.733
Mean (s.d.)	28.9 (9.3)	29.2 (9.9)			

d.f., degrees of freedom; s.d., standard deviation.

Table 2 Prevalence of childhood adversity in psychosis patients and unaffected controls

Type of childhood adversity	Patients (n=285) n (%)	Controls (n=256) n (%)	Unadjusted OR	95% CI	P	Adjusted OR[a]	95% CI	P
Parental separation	158 (56.0)	90 (35.3)	**2.34**	1.65–3.31	**<0.001**	**1.96**	1.32–2.91	**0.001**
Parental loss	33 (11.7)	16 (6.3)	**1.99**	1.06–3.71	**0.031**	1.99	0.98–4.06	0.058
Physical abuse	65 (22.8)	39 (15.3)	**1.63**	1.05–2.53	**0.029**	1.47	0.89–2.43	0.127
Sexual abuse	41 (14.4)	28 (11.0)	1.36	0.81–2.27	0.245	1.81	1.00–3.30	0.050

Bold text indicates result statistically significant at $P < 0.05$.
CI, confidence interval; OR, odds ratio.
a. Adjusted for gender, age at interview, ethnicity and level of education.

Table 3 Prevalence of familial risk in psychosis patients and unaffected controls

Type of familial risk	Patients (n=224) n (%)	Controls (n=250) n (%)	Unadjusted OR	95% CI	P	Adjusted OR[a]	95% CI	P
Family mental illness	94 (42.0)	70 (28.0)	**1.86**	1.27–2.73	**0.002**	**1.76**	1.14–2.70	**0.010**
Family psychosis	38 (17.3)	12 (5.1)	**3.90**	1.98–7.68	**<0.001**	**4.11**	1.94–8.72	**<0.001**
Parental mental illness	65 (29.5)	49 (20.8)	**1.60**	1.04–2.45	**0.031**	**1.56**	0.97–2.49	**<0.001**
Parental psychosis	28 (12.8)	8 (3.4)	**4.20**	1.87–9.43	**0.001**	**4.71**	1.90–11.67	**<0.001**

Bold text indicates result statistically significant at $P < 0.05$.
Mental illness includes psychosis, depression, and mania. Family refers to first-degree relatives.
CI, confidence interval; OR, odds ratio.
a. Adjusted for gender, age at interview, ethnicity and level of education.

Table 4 Association between parental mental illness and childhood adversity in psychosis patients and unaffected controls

Type of parental psychopathology	Childhood adversity present, n (%)	Childhood adversity absent, n (%)	Unadjusted OR	95% CI	P	Adjusted OR[a]	95% CI	P
Parental separation								
Psychosis patients	n = 119	n = 98						
Parental mental illness	34 (28.6)	30 (30.6)	0.91	0.50–1.63	0.743	1.02	0.53–1.94	0.955
Parental psychosis	13 (11.1)	14 (14.3)	0.75	0.33–1.68	0.485	1.01	0.40–2.52	0.986
Unaffected controls	n = 82	n = 153						
Parental mental illness	25 (30.5)	24 (15.7)	**2.36**	1.24–4.47	**0.009**	**2.58**	1.30–5.11	**0.007**
Parental psychosis	5 (6.1)	3 (2.0)	3.25	0.76–13.94	0.113	4.36	0.78–24.43	0.094
Parental loss								
Psychosis patients	n = 26	n = 190						
Parental mental illness	10 (38.5)	54 (28.4)	1.57	0.67–3.68	0.296	1.91	0.77–4.73	0.162
Parental psychosis	5 (19.2)	23 (12.2)	1.71	0.59–4.97	0.326	2.23	0.71–6.96	0.167
Unaffected controls	n = 16	n = 219						
Parental mental illness	2 (12.5)	47 (21.5)	0.52	0.11–2.38	0.402	0.56	1.12–2.65	0.463
Parental psychosis	0 (0.0)	8 (3.6)	–	–	–	–	–	–
Physical abuse								
Psychosis patients	n = 47	n = 173						
Parental mental illness	14 (29.8)	51 (29.5)	1.01	0.50–2.05	0.967	1.09	0.52–2.31	0.816
Parental psychosis	7 (14.9)	21 (12.3)	1.25	0.50–3.15	0.636	1.42	0.53–3.83	0.487
Unaffected controls	n = 38	n = 196						
Parental mental illness	15 (39.5)	34 (17.3)	**3.11**	1.47–6.57	**0.003**	**3.74**	1.68–8.33	**0.001**
Parental psychosis	3 (7.9)	5 (2.55)	3.27	0.75–14.33	0.115	4.54	0.93–22.18	0.061
Sexual abuse								
Psychosis patients	n = 29	n = 191						
Parental mental illness	10 (34.5)	55 (28.8)	1.30	0.57–2.98	0.533	1.24	0.53–2.89	0.625
Parental psychosis	2 (7.0)	26 (13.8)	0.46	0.10–2.07	0.315	0.46	0.10–2.11	0.317
Unaffected controls	n = 22	n = 212						
Parental mental illness	8 (36.4)	41 (19.3)	2.38	0.94–6.06	0.068	1.99	0.71–5.60	0.192
Parental psychosis	2 (9.1)	6 (2.8)	3.43	0.65–18.14	0.146	1.60	0.16–15.57	0.685

Bold text indicates result statistically significant at $P < 0.05$.
Mental illness includes psychosis, depression and mania.
CI, confidence interval; OR, odds ratio.
a. Adjusted for gender, age at interview, ethnicity and level of education; – indicates unable to calculate values due to at least one cell containing a zero value.

However, parental history of depression, mania or psychosis was more common among controls with, compared with those without, a history of parental separation and physical abuse, and these associations remained significant following adjustment for potential confounders. These results do not confirm the presence of a passive rGE, as a parental history of psychosis was associated with greater

odds of psychotic disorder but not with greater exposure to childhood adversity among patients in this sample.

Testing for confounding by parental psychopathology

Given that parental psychosis was shown to be strongly associated with psychosis case status, we investigated whether this form of familial risk could be a confounder in the original associations between childhood adversity and psychosis. As parental separation was the only form of adversity to be robustly associated with psychotic disorder we only investigated the impact on this association. The original association between parental separation and psychotic disorder (adjusted OR = 1.96, 95% CI: 1.32–2.91, $P = 0.001$) was only slightly attenuated when further adjusting for parental psychosis (adjusted OR = 1.64, 95% CI: 1.07–2.50, $P = 0.022$).

Interaction between familial liability and childhood adversity

The associations between each combination of childhood adversity and family or parental mental illness and psychotic disorder along with the results of the interaction analyses are presented in Table 5. Associations were evident between parental separation and psychotic disorder regardless of whether or not participants had a family or parental history of mental illness. There was a trend for associations between physical abuse, sexual abuse and psychosis to be stronger among those with no familial liability for mental

Table 5 The synergistic effects of childhood adversity and familial liability to mental illness on the presence of psychotic disorder

	Association with psychotic disorder					
Combination of risk factors	Unadjusted OR	95% CI	*P*	Adjusted OR[a]	95% CI	*P*
Parental loss (PL)						
No PL and no family mental illness (FMI)	[reference]	–	–	[reference]	–	–
PL only (FMI absent)	1.53	0.71–3.27	0.276	0.92	0.31–2.80	0.896
FMI only (PL absent)	1.20	0.81–1.78	0.354	1.12	0.67–1.89	0.664
Both PL and FMI present	**3.82**	1.24–11.73	**0.019**	2.57	0.70–9.36	0.153
	ICR: 2.09, 95% CI –2.29 to 6.47, *P*=0.350			ICR: 1.52, 95% CI –1.90 to 4.93, *P*=0.384		
No PL and no parental mental illness (PMI)	[reference]	–	–	[reference]	–	–
PL only (PM absent)	1.63	0.81–3.25	0.170	0.78	0.29–2.12	0.631
PMI only (PL absent)	1.14	0.73–1.76	0.566	0.89	0.49–1.61	0.693
Both PL and PMI present	**4.95**	1.07–22.88	**0.041**	4.85	0.91–25.64	0.063
	ICR: 3.18, 95% CI –4.43 to 10.80, *P*=0.412			ICR: 4.18, 95% CI –3.88 to 12.25, *P*=0.309		
Parental separation (PS)						
No PS and no family mental illness (FMI)	[reference]	–	–	[reference]	–	–
PS only (FM absent)	**3.09**	2.02–4.72	**<0.001**	**4.14**	2.19–7.81	**<0.001**
FMI only (PS absent)	**1.90**	1.13–3.20	**0.015**	**2.25**	1.11–4.54	**0.024**
Both PS and FM present	**2.33**	1.38–3.93	**0.002**	**2.20**	1.09–4.44	**0.028**
	ICR: –1.66, 95% CI –3.48 to 0.15, *P*=0.072			ICR: –3.18, 95% CI –6.33 to 0.01, *P*=0.047		
No PS and no parental mental illness (PMI)	[reference]	–	–	[reference]	–	–
PS only (PMI absent)	**2.86**	1.92–4.26	**<0.001**	**3.75**	2.09–6.75	**<0.001**
PMI only (PS absent)	**1.88**	1.08–3.41	**0.039**	**2.36**	1.04–5.36	**0.040**
Both PS and PMI present	**2.04**	1.14–3.64	**0.016**	1.62	0.75–3.51	0.224
	ICR: –1.70, 95% CI –3.53 to 0.14, *P*=0.069			ICR: –3.50, 95% CI –6.60 to 0.40, *P*=0.027		
Physical abuse (PA)						
No PA and no family mental illness (FMI)	[reference]	–	–	[reference]	–	–
PA only (FM absent)	**2.53**	1.43–4.48	**0.001**	1.69	0.74–3.88	0.212
FMI only (PA absent)	**1.63**	1.07–2.48	**0.023**	1.59	0.90–2.82	0.113
Both PA and FM present	1.18	0.61–2.30	0.622	0.80	0.34–1.91	0.617
	ICR: –1.97, 95% CI –3.74 to 0.21, *P*=0.028			ICR: –1.48, 95% CI –3.29 to 0.33, *P*=0.109		
No PA and no parental mental illness (PMI)	[reference]	–	–	[reference]	–	–
PA only (PMI absent)	**2.28**	1.34–3.86	**0.002**	1.53	0.71–3.30	0.280
PMI only (PA absent)	1.61	0.99–2.60	0.054	1.48	0.76–2.86	0.250
Both PA and PMI present	1.00	0.47–2.13	0.999	0.67	0.26–1.76	0.419
	ICR: –1.88, 95% CI –3.49 to –0.27, *P*=0.022			ICR: –1.33, 95% CI –3.00 to 0.34, *P*=0.118		
Sexual abuse (SA)						
No SA and no family mental illness (FMI)	[reference]	–	–	[reference]	–	–
SA only (FMI absent)	1.73	0.90–3.33	0.101	2.32	0.87–6.20	0.092
FMI only (SA absent)	1.41	0.95–2.11	0.091	1.33	0.78–2.28	0.298
Both SA and FMI present	1.19	0.54–2.66	0.663	1.33	0.46–3.81	0.596
	ICR: –0.95, 95% CI –2.49 to 0.60, *P*=0.231			ICR: –1.32, 95% CI –4.08 to 1.38, *P*=0.337		
No SA and no parental mental illness (PMI)	[reference]	–	–	[reference]	–	–
SA only (PMI absent)	1.52	0.83–2.76	0.172	2.30	0.96–5.51	0.062
PMI only (SA absent)	1.31	0.84–2.06	0.238	1.27	0.69–2.34	0.434
Both SA and PMI present	1.22	0.47–3.17	0.678	0.93	0.26–3.31	0.908
	ICR: –0.61, 95% CI –2.16 to –0.94, *P*=0.444			ICR: –1.64, 95% CI –4.09 to 0.80, *P*=0.188		

Bold text indicates result statistically significant at $P < 0.05$.
CI, confidence interval; ICR, interaction contrast ratio; OR, odds ratio.
a. Adjusted for gender, age at interview, ethnicity and level of education.

illness. However, there was no evidence of a positive additive interaction between these forms of childhood adversity and family history of mental illness.

Only for parental loss and familial liability was there suggestive evidence of departure from additivity (namely a stronger association with psychotic disorder for individuals with both a family psychiatric history and parental loss) but this failed to reach statistical significance.

Discussion

The present study investigated the role of different forms of childhood adversity and familial liability to mental illness, as well as the interaction between them, in the development of psychosis. The strongest associations between childhood adversity and psychotic disorder were found for parental separation, parental loss and physical abuse, in keeping with previous findings from an overlapping geographical area.[5,40] Moreover, within this sample, family history of mental illness was unsurprisingly a significant risk factor for psychotic disorder. Indeed, a history of psychosis in at least one parent was four times more common among participants with psychotic disorder than community controls. There was a smaller but significant association between current or past mental illness (psychosis, depression or mania) in a first-degree relative and clinical presentation of psychosis in this sample.

However, we did not find an association between parental history of psychosis and childhood adversity among the psychosis patients and, in keeping with these findings, controlling for parental history of psychosis only resulted in a small reduction in the strength of the association between parental separation and psychotic disorder. Therefore, our results could not confirm the presence of a potential passive rGE, in which parents pass on both a genetic liability to psychosis and create an abusive environment, which has been reported in a previous study.[27] An adoption design would be required to fully exclude the possibility of a passive rGE[16] operating in this association but suitable samples are rarely available. Unfortunately, it was not possible in the current study to explore other forms of rGE, namely evocative or active, for example, the child's genetic propensities eliciting harsher methods of physical punishment or making them more likely to select solitary environments.[16]

Moreover, there was no evidence for additive interactions between parental separation, physical abuse or sexual abuse in childhood and family psychiatric history in relation to the presence of psychotic disorder. This could suggest that these forms of childhood adversity may be associated with psychotic disorder independently of proxy genetic risk but might also reflect a lack of statistical power in this sample. Our findings are in line with previous studies reporting that the effect of childhood trauma on later experience of psychotic symptoms was independent of proxy genetic liability to psychosis.[1,26,27] However, our findings suggest that this may not be the case for parental loss. Overall, our results suggest that biological and environmental risk factors are both important in the aetiology of psychosis but the effects of some forms of childhood trauma might potentially act largely independently of pre-existing genetic liability to increase risk of psychosis.

Strengths and limitations

To our knowledge, this is the first study to explore the interplay between familial liability and various forms of childhood adversity in relation to the presence of psychotic disorder. This extends a previous report from our group that focused exclusively on maternal physical abuse.[27] The current study has several advantages, such as the inclusion of a sample of patients that had recently presented to mental health services with a psychotic disorder, thus extending previous reports that only examined psychotic symptoms or probable psychosis in the general population.[1,23–26] Our controls screened negative for psychotic disorder and had prevalence rates of childhood adversity similar to those reported in studies of the UK general population.[41] The proportion of patients reporting a first-degree relative with psychosis in this sample was 17.3% which is also within the range of existing studies.[20,27] Additionally, we used a standardised measure of adverse childhood experiences[32] and we were able to control for the potentially confounding effects of a range of demographic characteristics.

However, we had only 25% power to detect the 5% difference in proportions exposed to parental separation among individuals with a family history (n=162), compared with 100% power to detect the 27% difference in those without a family psychiatric history (n=308). Thus, we did not have enough power to test for interactions between childhood adversity and family psychiatric history in the association with psychotic disorder. Therefore, our findings should be interpreted with caution and need to be replicated in larger samples.

We also assessed childhood adversity using retrospective self-report that might have led to bias. Retrospective assessment is commonly used in studies investigating the role of childhood risk factors in psychosis as it avoids the high expense associated with following up a very large number of participants over several decades to obtain sufficient numbers with diagnosed psychosis. Although several studies have shown some bias in retrospective reports,[42] such bias is not considered sufficiently great to invalidate retrospective case-control studies of childhood experiences.[43] Moreover, previous studies have demonstrated that the effect of childhood adversity on psychosis remains significant regardless of the study design[44] and histories of childhood adversity obtained from psychosis patients appear remarkably reliable over time and unaffected by current symptoms.[3,4] We also attempted to enhance the validity of the self-reported experiences by utilising the CECA-Q[32] which elicits concrete examples of adverse experiences, has a manual to score the severity of the responses in a standardised manner (http://cecainterview.com/), and uses conservative cut-offs to ensure only severe adversity is considered in analyses. All of these factors increase the likelihood of an individual accurately remembering past adverse experiences.[43] However, if time had permitted it would have been preferable to conduct a more in-depth interview, such as the full Childhood Experience of Care and Abuse interview,[45] with participants to obtain more detailed information about their experiences and potentially further improve accuracy of reporting.[43]

Additionally, as only trauma occurring during childhood was investigated in this study, it is possible that other environmental risk factors such as cannabis use[46] or trauma occurring in adulthood[47] might demonstrate stronger associations with psychotic disorder and confound this relationship. Unfortunately, there was insufficient information within the GAP study to explore the role of cannabis use or adversity in adulthood in potentially modifying the childhood adversity-psychosis association. Ideally, large samples would allow inclusion of several environmental variables in the same model, such as cannabis use and preceding or subsequent adversity, in order to address this issue more comprehensively and to obtain a greater understanding of psychosis aetiology.

Finally, we used familial psychopathology as a proxy for genetic liability which may not have captured all of the relevant

genetic influences in the participants.[48] For instance, negative family history can include undeclared or unknown positive family history of mental illness. We supplemented the interviews with information obtained from clinical records (for the cases) but there are still likely to be familial cases that were missed. It is also possible that family members have a genetic propensity to developing mental health problems but this has not (yet) been phenotypically expressed. Family psychiatric history also captures familial effects of non-genetic origin.[17] However, the shared familial (non-genetic) component of schizophrenia risk is estimated to account for just a small proportion of the overall trait variance (4.5–11%).[10]

Unfortunately, it was not possible in the current study to adopt more sensitive measures of genetic risk.[49] Consequently, the impact of familial liability in this sample might have been underestimated and replication using more comprehensive molecular measures of genetic risk is needed. However, very large samples are required to identify sufficient common SNPs to explain a reasonable proportion of the genetic architecture of psychotic disorders and polygenic risk scores may not get us closer to understanding the specific mechanisms involved in G × E.[22] A recent study showed that the excess risk of offspring having schizophrenia in families affected by psychotic, bipolar affective or other psychiatric disorder is essentially unchanged when SNP-based variation is taken into account.[50] This provides some reassurance that the data obtained in the current study on psychiatric disorder in first-degree relatives had an adequate degree of accuracy. Nonetheless, future research using larger clinical samples and exploring whether measured genes moderate the impact of childhood adversity on the onset and course of psychotic disorders would be beneficial.

Clinical implications and further directions of research

Our results have implications for both clinical and research practices. Given that several forms of childhood adversity have been shown in the present study to be associated with psychotic disorder regardless of the presence or absence of familial liability, preventing trauma occurring or helping children to cope better in the aftermath of exposure could potentially help to prevent the onset of psychosis. Indeed, as recently shown by Kelleher *et al*,[51] the cessation of exposure to traumatic experiences might lead to a reduction in the incidence of psychotic experiences. Therefore, interventions focused on stopping childhood adversity or dealing with its consequences might have an impact not only on preventing the onset of psychosis but also on its longer-term course. Furthermore, research has shown that if the caregiver is perceived as unavailable, unresponsive and insensitive, this could lead to the development of an insecure attachment style in the child and to the child experiencing difficulties in relating to others.[52] Therefore, interventions focused on helping parents with psychosis and other severe mental health problems to develop better relationships with their families and/or providing family education and support could improve their children's attachment relationships and in turn, help children develop more positive relationships with others in adulthood.[52] Increased social networks and perceived support may reduce the likelihood of such children developing psychosis[53] and warrants further investigation.

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APPENDIX VI – Patient information form

SECTION 2 - Information Form *(not for data entry)*

You have been asked to take part in a study being conducted in the South London and Maudsley NHS Trust. Before you decide whether to enter the study, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information and ask any questions if something is not clear or you wish to know more.

TITLE OF PROJECT: GENETICS AND PSYCHIATRIC ILLNESS (GAP)

What are the aims of the study?

In our research project we are interested in identifying what the main risk factors that predispose to psychosis are. In particular, we want to know whether there are any genes that increase the risk of developing a psychotic disorder, either alone or by interacting with environmental factors such as stress, cannabis, and infections. Part of the reason why some people become ill may lay in genetic differences between people, in the same way that we are different in the colour of our eyes, hair etc. To achieve this, we will compare the genetic make-up of people with a diagnosis of psychosis with the make-up of people with similar characteristics but no history of mental health problems.

We also aim to establish whether some genes might influence the course of the illness and response to medication. Some patients experience an improvement of their psychiatric symptoms when they are treated with medications, whereas others do not do so well and/or experience severe side-effects. Therefore we aim to look at how genes can influence individual differences in response to drug treatment so that we may be able to choose better drugs for each person.

In conclusion, the type of genetic analysis that we carry out is only for research purposes and does not at present produce clinically relevant results.

Why are we asking for your help?

You have been invited to take part in this study because of the nature of the symptoms that you appear to have been experiencing. During the course of the study approximately 1000 people who have had symptoms like yours will be asked to take part.

What will we ask of you if you take part in the study?

For this project we will ask from you a small sample of blood, about 20 mls (a few tablespoons full) or cheek swab and saliva samples for metabolic and genetic analysis. We may also use your blood and saliva sample to:

1) **Measure the level of hormones and proteins contained in the blood serum and in the saliva.**
2) **Look at the expression of some genes of interest in the white cells contained in the blood.**

A medically trained researcher will take the blood sample using disposable sterile equipment. It will only take few minutes as for any routine blood sample. If you are unable or unwilling to give a blood sample it is also possible to perform genetic analysis from cheek swab samples, a simple procedure that (we can show you the kit and illustrate the procedure) collects dead cells present in your saliva and in your mouth. From the cheek swab sample we cannot measure level of medication or look at expression of genes, we can only extract a small amount of DNA. Therefore we prefer to ask for a blood sample to guarantee a better quality of our results and make the most out of your generous help.

A researcher will demonstrate how to collect the saliva sample and will provide you with the tubes required. The level of some proteins contained in the saliva can give us an indication of differences in the level of stress experienced by healthy volunteers and people suffering from mental illnesses.
We will also ask for some of your time to collect clinical and socio-demographic information using standardised research instruments: diagnostic interview, symptoms rating scale, socio-demographic interview and neuropsychological tests.

If you have already taken part in other research projects at the Institute of Psychiatry, London that involved some of the assessment we are interested in, we will not ask you to undergo them again but we request your permission to use the existing data.

Some people within the study will be invited to undergo an MRI scan of the head and of another region of the body (the adrenal gland, a small gland above the kidney). They will be presented with separate information and consent forms for this procedure.

The sample collection and the clinical assessment will require approximately 3 hours of your time. Moreover we would like to contact you again for follow up (up to 24 months) to repeat the above assessments to investigate changes over time. We will also reimburse any travel expense related to your participation into the study.

What are the risks?

The risks involved are those of ordinary blood tests such as small pain and occasionally a small bruise around the area from where the sample has been taken. There is no risk involved in the collection of saliva.

Is Confidentiality guaranteed?

All personal information about you is regarded as strictly confidential; only researchers belonging to the study team, and not external collaborators, know which sample belongs to whom. All the information about you will be coded; you will not be identifiable in any research outcome.

1) **The blood samples first and the DNA samples after extraction will be stored in the Institute of Psychiatry secured laboratory for 5 years.**
2) **The samples will be coded using bar codes (numbers and letters not referring to your name or date of birth) that will be entered on a secure computerized data base.**
3) **The clinical information collected on the sample will be securely held in the Institute of Psychiatry building.**

The access to the samples and the related information will be restricted to the researchers involved in the study. In case of commercial collaborations only the

coded data will be shared, therefore no researcher external to the study team will ever have access to personal data concerning participants.

Any future work will pursue aims related to the topic of this project and any extension of the project beyond 5 years, will be subject to review by a research ethics committee. You are free to withdraw from this study at any point without giving a reason by contacting the researcher whose details are at bottom of the consent form. Withdrawal will not affect any of the care and treatment you receive.

What are the benefits for you of taking part?

This is a research project, looking at comparing a group of healthy volunteers with people experiencing their first psychotic episode. As mentioned before, this study will not produce individual test results for any of the data collected. Therefore we cannot offer direct benefits for you. We will be able to provide all participants with a general summary of our research, when the project is complete, through a project newsletter. Our research study is also described on the Institute of Psychiatry general website (www.iop.kcl.ac.uk), under the Division of Psychological Medicine, Department of General Psychiatry.

Who is funding this project?

This study is funded by the The Maudsley Charitable Fund and the Department of Health.

Thank you very much for your time and once again please ask for more information on both the project and/or your illness/symptoms if it is still unclear.

Contact details for research team:

Dr Marta Di Forti
Institute of Psychiatry
Tel 020 7848 5352

email: m.diforti@iop.kcl.ac.uk

APPENDIX VII – Patient consent form

CONSENT FORM

If you have come to the decision to enter the study after carefully considering the information provided, please read and sign this form.

TITLE OF PROJECT: GENETICS AND PSYCHIATRIC ILLNESS (GAP)

Researcher: Dr Marta Di Forti, Institute of Psychiatry

1 **I have read the information sheet and I have been given a copy. I was given the opportunity to ask questions. I understand why the research is being done and the risks involved.**

Yes ☐[1] **No** ☐[2]

2 **I agree to give a sample of blood/cheek swab and saliva samples for research in the above project. I understand how the sample will be collected, that giving the sample is voluntary and that I am free to withdraw at any time without giving a reason, and without my medical treatment or legal rights being affected. I understand that I will be contacted in the future to repeat part of the assessment.**

Yes ☐[1] **No** ☐[2]

3 **I understand that research using the sample I give will involve genetic analysis aimed at understanding the role of genes in disease and response to drugs, that the data produced are for research rather than clinical purposes, and that these results will have no implications for me personally.**

Yes ☐[1] **No** ☐[2]

4 **I understand I will not receive any 'test' results from this study, because the assessment I will undergo, does not produce clinically relevant information but just research data. The project newsletter will describe the general importance of any research results obtained.**

Yes ☐[1] **No** ☐[2]

5 **I give permission for my previous research records to be looked at, and information from them to be analysed in strict confidence by responsible professional staff from the research team. Researchers external to the study team, collaborating in the project (including commercial collaborations) will only access my coded data.**

Yes ☐[1] **No** ☐[2]

6 **I agree that the samples I have given and the information gathered about me can be examined and stored(for 5 years) at the Institute of Psychiatry. I understand that future research may be performed by researchers other than those who conducted the first project, including researchers from commercial organisations. To guarantee confidentiality, I agree that researchers external to the study team, including those from commercial**

collaborators, will only have access to coded data and not to personal details. Any future research will only persue aims related to the topic of this project, and any extension of the project beyond 5 years, will be subjected to review by a research ethics committee.

Yes ☐1 **No** ☐2

7 **I consent to the input of coded data obtained from my blood sample and from the information gathered about me into a computer, to be used for statistical analysis and research. I understand I have the right to request, via the study co-ordinator, to review data concerning me, and to have such data modified if inaccurate, or deleted.**

Yes ☐1 **No** ☐2

8 **I understand I will not benefit financially if this research leads to the development of a new treatment or medical test but my travel expenses will be reimbursed.**

Yes ☐1 **No** ☐2

.....	.....	.....
Name of subject	**Date**	**Signature**

.....	.....	.....
Name of researcher	**Date**	**Signature**

Would you like to be sent further information about

the project in our newsletter?

Yes ☐1 **No** ☐2

Contact details for research team:

Dr Marta Di Forti
Institute of Psychiatry
Tel 020 7848 5352

email: m.diforti@iop.kcl.ac.uk

APPENDIX VIII – Control information form

SECTION I - Information Form *(not for data entry)*

You have been asked to take part in a study being conducted in the South London and Maudsley NHS Trust. Before you decide whether to enter the study, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information and ask any questions if something is not clear or you wish to know more.

TITLE OF PROJECT: GENETICS AND PSYCHIATRIC ILLNESS (GAP)

What are the aims of the study?

In our research project we are interested in identifying what the main risk factors that predispose to psychosis are. In particular, we want to know whether there are any genes that increase the risk of developing a psychotic disorder, either alone or by interacting with environmental factors such as stress, cannabis, and infections. Part of the reason why some people become ill may lay in genetic differences between people, in the same way that we are different in the colour of our eyes, hair etc. To achieve this, we will compare the genetic make-up of people with a diagnosis of psychosis with the make-up of people with similar characteristics but no history of mental health problems.

We also aim to establish whether some genes might influence the course of the illness and response to medication. Some patients experience an improvement of their psychiatric symptoms when they are treated with medications, whereas others do not do so well and/or experience severe side-effects. Therefore we aim to look at how genes can influence individual differences in response to drug treatment so that we may be able to choose better drugs for each person.

In conclusion, the type of genetic analysis that we carry out is only for research purposes and does not at present produce clinically relevant results.

Why are we asking for your help?

We invite healthy volunteers (control subjects), such as you, to participate in order to compare your genes with those of volunteer patients with psychiatric illness.

What will we ask of you if you take part in the study?

For this project we will ask from you a small sample of blood, about 20 mls (a few tablespoons full) or cheek swab and saliva samples for metabolic and genetic analysis. We may also use your blood and saliva sample to:

1) **Measure the level of hormones and proteins contained in the blood serum and in the saliva.**
2) **Look at the expression of some genes of interest in the white cells contained**

in the blood.

A medically trained researcher will take the blood sample using disposable sterile equipment. It will only take few minutes as for any routine blood sample. If you are unable or unwilling to give a blood sample it is also possible to perform genetic analysis from cheek swab samples, a simple procedure that (we can show you the kit and illustrate the procedure) collects dead cells present in your saliva and in your mouth. From the cheek swab sample we cannot measure level of medication or look at expression of genes, we can only extract a small amount of DNA. Therefore we prefer to ask for a blood sample to guarantee a better quality of our results and make the most out of your generous help.

A researcher will demonstrate how to collect the saliva sample and will provide you with the tubes required. The level of some proteins contained in the saliva can give us an indication of differences in the level of stress experienced by healthy volunteers and people suffering from mental illnesses.

We will also ask for some of your time to collect clinical and socio-demographic information using standardised research instruments: diagnostic interview, socio-demographic interview and neuropsychological tests.

If you have already taken part in other research projects at the Institute of Psychiatry, London that involved some of the assessment we are interested in, we will not ask you to undergo them again but we request your permission to use the existing data.

Some people within the study will be invited to undergo an MRI scan of the head and of another region of the body (the adrenal gland, a small gland above the kidney). They will be presented with separate information and consent forms for this procedure.

The sample collection and the clinical assessment will require approximately 3 hours of your time. Moreover we would like to contact you again for follow up (up to 24 months) to repeat the above assessments to investigate changes over time. We will also reimburse any travel expense related to your participation into the study.

What are the risks?

The risks involved are those of ordinary blood tests such as small pain and occasionally a small bruise around the area from where the sample has been taken. There is no risk involved in the collection of saliva.

Is Confidentiality guaranteed?

All personal information about you is regarded as strictly confidential; only researchers belonging to the study team, and not external collaborators, know which sample belongs to whom. All the information about you will be coded; you will not be identifiable in any research outcome.

1) **The blood samples first and the DNA samples after extraction will be stored in the Institute of Psychiatry secured laboratory for 5 years.**
2) **The samples will be coded using bar codes (numbers and letters not referring to your name or date of birth) that will be entered on a secure**

computerized data base.

3) **The clinical information collected on the sample will be securely held in the Institute of Psychiatry building.**

The access to the samples and the related information will be restricted to the researchers involved in the study. In case of commercial collaborations only the coded data will be shared, therefore no researcher external to the study team will ever have access to personal data concerning participants.

Any future work will pursue aims related to the topic of this project and any extension of the project beyond 5 years, will be subject to review by a research ethics committee. You are free to withdraw from this study at any point without giving a reason by contacting the researcher whose details are at bottom of the consent form. Withdrawal will not affect any of the care and treatment you receive.

What are the benefits for you of taking part?

This is a research project, looking at comparing a group of healthy volunteers with people experiencing their first psychotic episode. As mentioned before, this study will not produce individual test results for any of the data collected. Therefore we cannot offer direct benefits for you. We will be able to provide all the participants with a general summary of our research, when the project is complete, through a project newsletter. Our research study is also described on the Institute of Psychiatry general website (www.iop.kcl.ac.uk), under the Division of Psychological Medicine, Department of General Psychiatry.

Who is funding this project?
This study is funded by the The Maudsley Charitable Fund and the Department of Health.

Thank you very much for your time and once again please ask for more information on both the project and/or your illness/symptoms if it is still unclear.

Contact details for research team: Dr

Marta Di Forti
Institute of Psychiatry
Tel 020 7848 5352
email: m.diforti@iop.kcl.ac.uk

APPENDIX IX – Control consent form

CONSENT FORM

If you have come to the decision to enter the study after carefully considering the information provided, please read and sign this form.

TITLE OF PROJECT: GENETICS AND PSYCHIATRIC ILLNESS (GAP)

Researcher: Dr Marta Di Forti, Institute of Psychiatry

		Yes	No
1)	I have read the information sheet and I have been given a copy. I was given the opportunity to ask questions. **I understand why the research is being done and the risks involved**.	☐1	☐2
2)	**I agree to give a sample of blood/cheek swab and saliva samples** for research in the above project. I understand how the sample will be collected, that giving the sample is voluntary and that I am free to withdraw at any time without giving a reason, and without my medical treatment or legal rights being affected. I understand that I will be contacted in the future to repeat part of the assessment.	☐1	☐2
3)	**I understand that research using the sample I give will involve genetic analysis** aimed at understanding the role of genes in disease and response to drugs, that the data produced are for research rather than clinical purposes, and that these results will have no implications for me personally.	☐1	☐2
4)	**I understand I will not receive any 'test' results from this study**, because the assessment I will undergo, does not produce clinically relevant information but just research data. The project newsletter will describe the general importance of any research results obtained.	☐1	☐2
5)	**I give permission for my previous research records to be looked at, and information from them to be analysed in strict confidence by responsible professional staff from the research team**. Researchers external to the study team, collaborating in the project (including commercial collaborations) will only access my coded data.	☐1	☐2
6)	**I agree that the samples I have given and the information gathered about me can be examined and stored (for 5 years) at the Institute of Psychiatry.** I understand that future research may be performed by researchers other than those who conducted the first project, including researchers from commercial organisations. To guarantee confidentiality, I agree that researchers external to the study team, including those from commercial collaborators, will only have access to coded data and not to personal details. Any future research will only pursue aims related to the topic of this project, and any extension of the project beyond 5 years, will be subjected to review by a research ethics committee.	☐1	☐2
7)	**I consent to the input of coded data obtained from my blood sample and from the information gathered about me into a computer, to be used for statistical analysis and research.** I understand I have the right to request, via the study co-ordinator, to review data concerning me, and to have such data modified if inaccurate, or deleted.	☐1	☐2

8) **I understand I will not benefit financially** if this research leads to the development of a new treatment or medical test but my travel expenses will be reimbursed. ☐1 ☐2

9) **I give permission for my GP records to be looked at.** ☐1 ☐2

10) **I agree to my mother being approached to participate in this study.** ☐1 ☐2

Contact details:

Name …….

Address …….....

…….

Phone Number ……

11) **I agree to a sibling being approached to participate in this study.** ☐1 ☐2

Contact details:

Name …….

Address …….....

…….

Phone Number ……

……	……..	……
Name of Subject	**Date**	**Signature**
……	……..	……
Name of Researcher	**Date**	**Signature**

	Yes	No
Would you like to be sent further information about the project in our newsletter?	☐1	☐2

Contact details for research team:

Dr Marta Di Forti
Institute of Psychiatry
Tel 020 7848 5352
e-mail: marta.diforti@kcl.ac.uk

APPENDIX X – Global Assessment of Functioning Scales

12.1 GAF Scale - a) SYMPTOMS

Instructions to researcher: *Consider psychological functioning on a hypothetical continuum of mental health-illness. Rate symptoms over the* ***last 7 days before interview****.*

100-91 ☐[1]
No symptoms

90-81 ☐[2]
Absent or minimal symptoms (e.g. mild anxiety before an exam)

80-71 ☐[3]
If symptoms are present they are transient and expectable reactions to psychosocial stresses (e.g. difficulty concentrating after family argument)

70-61 ☐[4]
Some mild symptoms (e.g. depressed mood and mild insomnia)

60-51 ☐[5]
Moderate symptoms (e.g. flat affect and circumstantial speech, occasional panic attacks)

50-41 ☐[6]
Serious symptoms (e.g. suicide ideation, severe obsessional rituals, frequent shoplifting)

40-31 ☐[7]
Some impairment in reality testing or communication (e.g. speech is at times illogical, obscure or irrelevant)

30-21 ☐[8]
Behaviour is considered influenced by delusions or hallucinations OR serious impairment in communications or judgment (e.g. sometimes incoherent, acts grossly inappropriately, suicidal preoccupation)

20-11 ☐[9]
Some danger or hurting self or others (e.g. suicide attempts without clear expectation of death, frequently violent, manic excitement) OR gross impairment in communication (e.g. largely incoherent or mute)

10-1 ☐[10]
Persistent danger of severely hurting self or others (e.g. recurrent violence), serious suicidal act with clear expectation of death

b) Please score with the nearest 5 (if score 34, score 35; if 12 score 10 etc) as it simplifies data analysis.

Rating: .....

12.2 GAF Scale - a) DISABILITY

Instructions to researcher: *Consider psychological, social and occupational functioning on a hypothetical continuum of mental health-illness. Do not include impairment of function due to physical or environmental limitations. Rate functioning over the* ***last 7 days before interview.***

100-91 ☐[1]
Superior functioning in a wide range of activities; life's problems never get out of hand; is sought out by others because of his/her positive qualities

90-81
Good functioning in all areas, interested and involved in a wide range or activities, socially effective, generally satisfied with life, no more than everyday problems or concerns (e.g. an occasional argument with family members) ☐[2]

80-71
No more than slight impairment in social, occupational, or school functioning (e.g. temporarily falling behind in school work) ☐[3]

70-61
Some difficulty in social, occupational, or school functioning (e.g. occasional truancy, or theft within the household), but generally functioning pretty well, has some meaningful interpersonal relationships ☐[4]

60-51
Moderate difficulty in social, occupational, or school functioning (e.g. few friends, conflicts with co-workers) ☐[5]

50-41
Any serious impairment in social, occupational, or school functioning (e.g. no friends, unable to keep a job) ☐[6]

40-31
Major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood (e.g. expressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school) ☐[7]

30-21
Inability to function in almost all areas (e.g. stays in bed all day; no job, home or friends) ☐[8]

20-11
Occasionally fails to maintain minimal personal hygiene (e.g. smears faeces) OR gross impairment in communication (e.g. largely incoherent or mute) ☐[9]

10-1
Persistent inability to maintain minimum personal hygiene ☐[10]

b) Please score with the nearest 5 (if score 34, score 35; if 12 score 10 etc) as it simplifies data analysis

Rating: .....

Reference: Endicott, J., Spitzer, R.L., Fleiss, J.L., Cohen, J. (1976). The Global Assessment Scale. A procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry*, *33*, 766–771.

APPENDIX XI – PANSS

SECTION 8 - PANSS

Rater's Initials: *Date of Completion: ...../...../*

Not assessed/missing -66 *Participant refused to answer* -88

Instructions to researcher: ***Tick the box for each symptom which best describes the participant's condition*** *over the last 7 days* ***and not relative to any other time. For more detailed information on each PANSS item, and to make ratings, you should use the PANSS Manual of Definitions***

POSITIVE SCALE		Absent	Minimal	Mild	Moderate	Moderate Severe	Severe	Extreme
8.1	Delusions	1	2	3	4	5	6	7
8.2	Conceptual disorganization	1	2	3	4	5	6	7
8.3	Hallucinatory behaviour	1	2	3	4	5	6	7
8.4	Excitement	1	2	3	4	5	6	7
8.5	Grandiosity	1	2	3	4	5	6	7
8.6	Suspiciousness / persecution	1	2	3	4	5	6	7
8.7	Hostility	1	2	3	4	5	6	7

NEGATIVE SCALE		Absent	Minimal	Mild	Moderate	Moderate Severe	Severe	Extreme
8.8	Blunted affect	1	2	3	4	5	6	7
8.9	Emotional withdrawal	1	2	3	4	5	6	7
8.10	Poor rapport	1	2	3	4	5	6	7
8.11	Passive/apathetic Social withdrawal	1	2	3	4	5	6	7
8.12	Difficulty in abstract thinking	1	2	3	4	5	6	7
8.13	Lack of spontaneity and Flow of conversation	1	2	3	4	5	6	7
8.14	Stereotyped thinking	1	2	3	4	5	6	7

GENERAL PSYCHOPATHOLOGY SCALE		Absent	Minimal	Mild	Moderate Severe	Moderate	Severe	Extreme
8.15	Somatic concern	1	2	3	4	5	6	7
8.16	Anxiety	1	2	3	4	5	6	7
8.17	Guilt Feelings	1	2	3	4	5	6	7
8.18	Tension	1	2	3	4	5	6	7
8.19	Mannerisms and Posturing	1	2	3	4	5	6	7
8.20	Depression	1	2	3	4	5	6	7
8.21	Motor Retardation	1	2	3	4	5	6	7
8.22	Uncooperativeness	1	2	3	4	5	6	7
8.23	Unusual thought content	1	2	3	4	5	6	7
8.24	Disorientation	1	2	3	4	5	6	7
8.25	Poor attention	1	2	3	4	5	6	7
8.26	Lack of judgment and insight	1	2	3	4	5	6	7
8.27	Disturbance of volition	1	2	3	4	5	6	7
8.28	Poor impulse control	1	2	3	4	5	6	7
8.29	Preoccupation	1	2	3	4	5	6	7
8.30	Active social avoidance	1	2	3	4	5	6	7
		1	2	3	4	5	6	7

Reference: Kay, S.R., Fiszbein, A., Opler, L.A. (1987). The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*, *13*, 507–518.

APPENDIX XII – Psychosis Screening Questionnaire (PSQ)

GAP/IMPACT		ID NUMBER: _
SUBJECT'S INITIALS: _ _ RATER'S INITIALS: _ _	DATE OF COMPLETION: _ _ / _ _ _ / _ _ _ _	STUDY PERIOD: _ _ 00=Baseline

Psychosis screening questionnaire

Code: No = 0 Unsure = 1 Yes = 2

In this health survey we have to ask about a whole range of experiences. Some of these experiences are quite rare. However, I would be very much obliged if you would bear with us and answer the questions I am going to ask you now.

Q1. Over the past year, have there been times when you felt very happy indeed without a break for days on end? ☐

(a) Was there an obvious reason for this? ☐

(b) Did your relatives or friends think it was strange or complain about it? ☐ **If 2 stop**

Q2. Over the past year, have you ever felt that your thoughts were directly interfered with or controlled by some outside force or person? ☐

(a) Did this come about in a way that many people would find hard to believe, for instance through telepathy? ☐ **If 2 stop**

No = 0 Unsure = 1 Yes = 2

Q3. Over the past year, have there been times when you felt that people were against you? ☐

(a) Have there been times when you felt that people were deliberately acting to harm you or your interests? ☐

(b) Have there been times when you felt that a group of people was plotting to cause you serious harm or injury? ☐ **If 2 stop**

Q4. Over the past year have there been times when you felt that something strange was going on? ☐

(a) Did you feel it was so strange that people would find it very hard to believe? ☐ **If 2 stop**

Q5. Over the past year, have there been times when you heard or saw things that other people couldn't ☐ **If 1 or 2 stop**

(a) Did you at any time hear voices saying quite a few words or sentences when there was no-one around that might account for it? ☐ **If 2 stop**

Q6. Have you ever received treatment for any psychiatric or psychological problem?

……

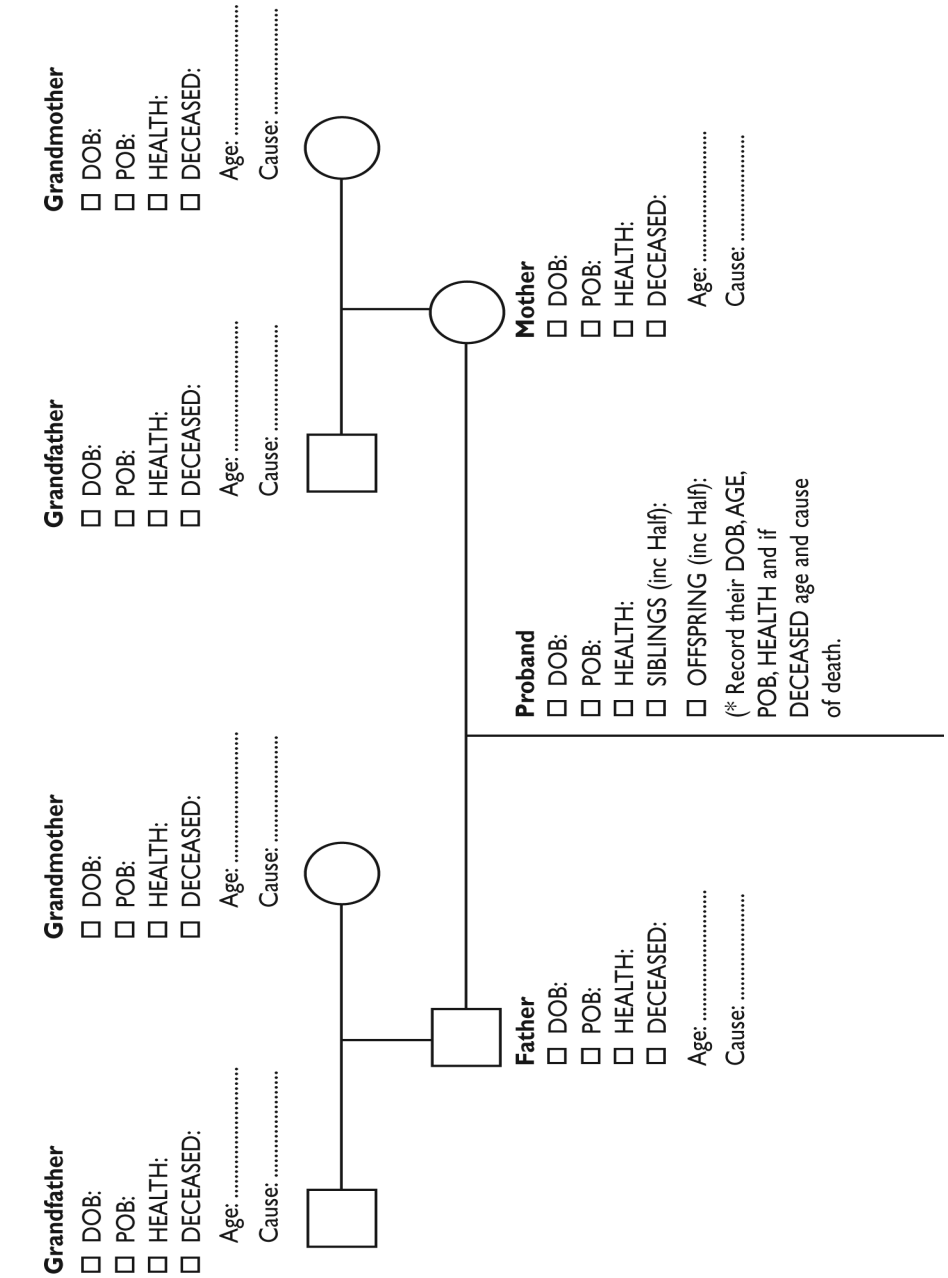
……..

Reference: Bebbington, P., Nayani, T. (1995). The Psychosis Screening Questionnaire. *Int J Methods Psychiatr Res*, *5*, 11–20.

General Screening Questions *(not for data entry)*

28.1 Let's go over your family

Draw family tree on the table below *(Include Grandparents, parents, siblings and offspring aged 18 or above)*



28.2 Now I am asking you to keep in mind all those in your family as I go through this list of questions *(Note all positive responses on the pedigree)*

Did anyone:

a) Feel very low for a couple of weeks or more, or have a diagnosis of depression?

Yes ☐[1] No ☐[2] If **YES**, who? .....

b) Attempt or complete suicide?

Yes ☐[1] No ☐[2] If **YES**, who? .....

c) Seem overexcited (or manic) day and night, or have a diagnosis of mania?

Yes ☐[1] No ☐[2] If **YES**, who? .....

d) Have visions, hear voices, or have beliefs that seem strange or unreal?

Yes ☐[1] No ☐[2] If **YES**, who? .....

e) Have unusual or bizarre behavior, or have a diagnosis of schizophrenia?

Yes ☐[1] No ☐[2] If **YES**, who? .....

f) Was anyone hospitalized for psychiatric problems?

Yes ☐[1] No ☐[2] If **YES**, who? .....

28.3 For each of these given a positive response in the General Screening, complete the symptom checklist for any suspected: Depression/Mania, Psychosis, or Paranoid/Schizoid/Schizotypal Personality

DEPRESSION CHECKLIST

Instructions to researcher: *Code for a single episode (best recalled, worst episode if possible).*

Relationship of family member to participant: .....

		No	Yes	Unknown
28.4	**During depression:**			
a)	Was he/she depressed most of the day, nearly every day, for as long as a week or more?	☐ 0	☐ 1	☐ 9
b)	Did he/she lose interest in things or become unable to enjoy most things, for as long as a week?	☐ 0	☐ 1	☐ 9
c)	Did he/she have a change in appetite or weight without trying to?	☐ 0	☐ 1	☐ 9
d)	Did he/she have a change in sleep patterns (either too much or too little)?	☐ 0	☐ 1	☐ 9
e)	Did he/she become unable to work, go to school, or take care of household responsibilities?	☐ 0	☐ 1	☐ 9

If **YES**: please describe: .....

.....

*If **NO** to all of a - e, please go to 28.11*

f)	Did he/she move or speak more slowly than usual?	☐ 0	☐ 1	☐ 9
g)	Did he/she pace or wring his/her hands?	☐ 0	☐ 1	☐ 9
h)	Did he/she have less energy or feel tired out?	☐ 0	☐ 1	☐ 9
i)	Did he/she feel guilty, worthless or blame himself/herself?	☐ 0	☐ 1	☐ 9
j)	Did he/she have trouble concentrating or making decisions?	☐ 0	☐ 1	☐ 9
k)	Did he/she talk of death or suicide? Or try suicide?	☐ 0	☐ 1	☐ 9
l)	Did he/she have visions, or hear voices, or have beliefs or behavior that seem strange or unusual, at the same time as (symptoms above)?	☐ 0	☐ 1	☐ 9

*(If **YES**, complete a Psychosis Checklist after this one.)*

Code Response

28.5 Code and describe professional treatment:

None	☐ 0	
Inpatient:	☐ 1	.....
Outpatient	☐ 2	.....
ECT	☐ 3	.....
Medication	☐ 4	.....
Unknown	☐ 9	

28.6 Age of onset .....

28.7 Number of episodes .....

28.8 Duration of longest episode in weeks .....

Code Response

28.9 Rate and code impairment or incapacitation:

None	□ 0
Modified RDC Impairment	□ 1
Modified RDC Incapacitation	□ 2
RDC Minor Role Dysfunction	□ 3
Change from previous functioning	□ 4
Unknown	□ -77

28.10 Interviewer judgment on reliability of this information:

Good	□ 1
Fair	□ 2
Poor	□ 3

MANIA CHECKLIST

Relationship of family member to participant: .....

28.11 For most of the time day and night over several days, did he/she (more than usual):	No	Yes	Unknown
a) Seem too happy/high/excited?	□ 0	□ 1	□ 9
b) Become so excited or agitated it was impossible to converse with him/her?	□ 0	□ 1	□ 9
c) Act very irritable or angry?	□ 0	□ 1	□ 9
d) Need less sleep without feeling tired?	□ 0	□ 1	□ 9
e) Show poor judgment (e.g., spending sprees, sexual indiscretions?)	□ 0	□ 1	□ 9

If **YES**: please describe:

.....

.....

*If **NO** to all of a - e, please go to 28.18*

f) Behave in such a way as to cause difficulty for those around him/her (obnoxious/manipulative)?	□ 0	□ 1	□ 9
g) Feel that he/she had special gifts or powers?	□0	□1	□9
h) Become more talkative than usual?	□0	□1	□9
i) Jump from one idea to another?	□0	□1	□9
j) Become easily distracted?	□0	□1	□9
k) Get involved in too many activities at work or school?	□0	□1	□9
l) Have visions? Hear voices? Have beliefs or behavior that seem strange or unusual? At the same time as (above symptoms)? *(If **YES**, complete a Psychosis Checklist after this one.)*	⊓0	⊓1	⊓9

Code Response

28.12 Code and describe professional treatment:

None	□ 0	
Inpatient:	□ 1	.....
Outpatient	□ 2	.....
ECT	□ 3	.....
Medication	□ 4	.....
Unknown	□ 9	

28.13 Age of onset .....

28.14 Number of episodes .....

28.15 Duration of longest episode in weeks.....

Code Response

28.16 Rate and code impairment or incapacitation:

None	□	0
Impaired	□	1
Incapacitated	□	2
Unknown	□	-77

28.17 Interviewer judgment on reliability of this information:

Good	□	1
Fair	□	2
Poor	□	3

e) PSYCHOSIS

Instructions to researcher: *Code for a single episode (best recalled, worst episode if possible).*

Relationship of family member to participant: .....

28.18 What were his/her unusual beliefs or experiences?

Please describe: .....

.....

Did he/she ever:	No	Yes	Unknown
a) Believe people were following him/her, or that someone was trying to hurt or poison him/her?	☐ 0	☐ 1	☐ 9
b) Believe someone was reading his/her mind?	☐ 0	☐ 1	☐ 9
c) Believe he/she was under the control of some outside person or power or force?	☐ 0	☐ 1	☐ 9
d) Believe his/her thoughts were broadcast, or that an outside force took away his/her thoughts or put thoughts into his/her head?	☐ 0	☐ 1	☐ 9
e) Have any other strange or unusual beliefs?	☐ 0	☐ 1	☐ 9

If **YES**: please describe: .....

.....

f) See things that were not really there?	☐ 0	☐ 1	☐ 9
g) Hear voices or other sounds that were not real?	☐ 0	☐ 1	☐ 9

If **YES**: please describe: .....

.....

i) Code **YES** if: voice with content having no relation to depression or elation, or voice keeping up running commentary on subject's behavior or thoughts, or two or more voices conversing.)	☐ 0	☐ 1	☐ 9
h) Speak in a way that was difficult to make sense of?	☐ 0	☐ 1	☐ 9

If **YES**: please describe:

.....
.....

i) Seem to be physically stuck in one position, or move around excitedly without any purpose?	☐ 0	☐ 1	☐ 9
j) Appear to have no emotions, or inappropriate emotions?	☐ 0	☐ 1	☐ 9

28.19 How long did the longest of these experiences last? .....

Instructions to researcher: *If less than 1 week (unless successfully treated), STOP HERE. Otherwise continue, if informant is knowledgeable about this person. If subject did NOT have any episode of Major Depression or Mania (by FIGS checklists from this informant), go to question 28.24.*

	No	Yes	Unknown
28.20 When any (SX above) happened, did he/she also have the mood disturbance we discussed before, at the same time?	☐ 0	☐ 1	☐ 9

*If **NO**, go to question 28.24*

	No	Yes	Unknown
28.21 (Probe and code YES if mania and/or depression lasted at least 30% of total duration of illness described above, or medication for it.)	☐ 0	☐ 1	☐ 9
28.22 (Probe and code YES if illness described above or medication for it, was ever present for as long as one week, without depression and/or mania.)	☐ 0	☐ 1	☐ 9

*If **NO**, go to question 28.24*

28.23 (Code YES if the above was true for as long as two weeks.)	☐ 0	☐ 1	☐ 9

Code Response

28.24 Code and describe professional treatment:

None	☐ 0
Inpatient:	☐ 1 .....
Outpatient	☐ 2.....
ECT	☐ 3.....
Medication	☐ 4 .....
Unknown	☐ 9

28.25 Age of onset .....

28.26 Number of episodes .....

28.27 Duration of longest episode in weeks..... Code Response

28.28 Rate and code impairment or incapacitation:

None	☐ 0
Impaired	☐ 1
Incapacitated	☐ 2
Unknown	☐ -77

Instructions to researcher: *If informant apparently does not know subject well enough to give information on Prodromal/Residual symptoms, STOP HERE. If duration criterion for DSM III-R Schizophrenia, Chronic Type, already met, (question 9, total illness duration > 2 years), STOP HERE.*

28.29 Interviewer judgment on reliability of this information:

Good	□[1]
Fair	□[2]
Poor	□[3]

Instructions to researcher: *Use this page only if Schizo-affective is ruled out (by questions 3 to 5 above), or if the psychosis symptoms lasted at least one week (or shorter duration if successfully treated).*

PSYCHOSIS
Establishing the Prodromal Period:

28.30 Prodromal period: Now I would like to ask you about the year before his/her (psychotic symptoms) started. During that time did he/she…

Residual period: Now I would like to ask you about the year after his/her (psychotic symptoms) stopped. During that time did he/she…

		Prodromal Period			Residual Period		
		No	Yes	Unknown	No	Yes	Unknown
a)	Stay away from family and friends, become socially isolated?	□[0]	□[1]	□[9]	□[0]	□[1]	□[9]
b)	Have trouble doing his/her job, going to school, or doing work at home?	□[0]	□[1]	□[9]	□[0]	□[1]	□[9]
c)	Do something peculiar like talking to self in public?	□[0]	□[1]	□[9]	□[0]	□[1]	□[9]
d)	Appear to have no emotions or inappropriate emotions?	□[0]	□[1]	□[9]	□[0]	□[1]	□[9]
e)	Speak in a way that was hard to understand, or was he/she at a loss for words?	□[0]	□[1]	□[9]	□[0]	□[1]	□[9]
f)	Have unusual beliefs or ideas?	□[0]	□[1]	□[9]	□[0]	□[1]	□[9]
g)	Have unusual perceptions, like sensing the presence of a person not actually present?	□[0]	□[1]	□[9]	□[0]	□[1]	□[9]
h)	Have no interests, no energy?	□[0]	□[1]	□[9]	□[0]	□[1]	□[9]
i)	Find special meaning in TV, radio, or newspaper articles?	□[0]	□[1]	□[9]	□[0]	□[1]	□[9]
j)	Feel nervous with other people?	□[0]	□[1]	□[9]	□[0]	□[1]	□[9]
k)	Worry that people were out to get him/her?	□[0]	□[1]	□[9]	□[0]	□[1]	□[9]

28.31 **a)** How long did he/she have these experiences? ..... weeks

INTERVIEWER: *Return to top of question 28.30 to establish the Residual period and code in Residual Column.*

b) How long did he/she have these experiences after his/her (Active psychotic features) stopped?

..... weeks

	No	Yes	Unknown
28.32 Was he/she always this way?	□0	□1	□9

Code based on Informant's Report:

Did person being described have:	No	Yes	Unknown
a) Depression	□0	□1	□9
i) Single	□0	□1	□9
ii) Recurrent	□0	□1	□9
iii) Impaired/Incapacitated	□0	□1	□9
iv) Treatment	□0	□1	□9
v) Age of onset			
b) Mania	□0	□1	□9
i) Single	□0	□1	□9
ii) Recurrent	□0	□1	□9
iii) Impaired/Incapacitated	□0	□1	□9
iv) Treatment	□0	□1	□9
v) Age of onset			
c) Psychosis	□0	□1	□9
i) Chronic	□0	□1	□9
ii) Acute?	□0	□1	□9
iii) Outside of mood disorder	□0	□1	□9
iv) Treatment	□0	□1	□9
v) Age of onset			

Reference: NIMH Genetics Initiative (1992). *Family Interview for Genetic Studies (FIGS)*. Rockville, MD: National Institute of Mental Health.

APPENDIX XIV – Shortened CECA-Q

6.19 Who brought you up before age 17?

Instructions to researcher: *Write below the PARENT FIGURES who brought participant up in childhood. List each family arrangement with different types of parent figures which* ***lasted a year or longer****. Consider natural parents, step parents (including parents' live in partners), aunt, friends of the family, adoptive parents, foster parents, etc.*

If participant has only lived in one arrangement, then fill in the first family arrangement and leave the other boxes blank. For example, if this was with their biological parents, tick 'natural mother' and 'natural father' and write in age '0'.

If they have lived in other arrangements that lasted a year or longer such as with mother alone or mother and step-father, then list them a second/third etc family arrangement together with age they were when the arrangement began.

a) First Family Arrangement *(all)*

i) Mother figure:

Natural mother	□[1]	Other non-relative e.g. foster/adoptive/godmother	□[4]
Step-mother/father's live-in partner	□[2]	Other	□[5]
Other relative e.g. aunty, grandmother	□[3]	No mother figure	□[6]

ii) Father figure:

Natural father	□[1]	Other non-relative e.g. foster/adoptive/godfather	□[4]
Step-father/ mother's live-in partner	□[2]	Other	□[5]
Other relative e.g. uncle, grandfather	□[3]	No father figure	□[6]

iii) Your age at start: ..... years

b) Second Family Arrangement *(if applicable)*

i) Mother figure:

Natural mother	□[1]	Other non-relative e.g. foster/adoptive/godmother	□[4]
Step-mother/father's live-in partner	□[2]	Other	□[5]
Other relative e.g. aunty, grandmother	□[3]	No mother figure	□[6]

ii) Father figure:

Natural father	□[1]	Other non-relative e.g. foster/adoptive/godfather	□[4]
Step-father/ mother's live-in partner	□[2]	Other	□[5]
Other relative e.g. uncle, grandfather	□[3]	No father figure	□[6]

iii) Your age at start: ..... years

c) Third Family Arrangement *(if applicable)*

i) Mother figure:

Natural mother	□[1]	Other non-relative e.g. foster/adoptive/godmother	□[4]
Step-mother/father's live-in partner	□[2]	Other	□[5]
Other relative e.g. aunty, grandmother	□[3]	No mother figure	□[6]

ii) Father figure:

Natural father	□[1]	Other non-relative e.g. foster/adoptive/godfather	□[4]
Step-father/ mother's live-in partner	□[2]	Other	□[5]
Other relative e.g. uncle, grandfather	□[3]	No father figure	□[6]

iii) Your age at start: ..... years

d) Fourth Family Arrangement *(if applicable)*

i) Mother figure:

Natural mother	□[1]	Other non-relative e.g. foster/adoptive/godmother	□[4]
Step-mother/father's live-in partner	□[2]	Other	□[5]
Other relative e.g. aunty, grandmother	□[3]	No mother figure	□[6]

ii) Father figure:

Natural father	□[1]	Other non-relative e.g. foster/adoptive/godfather	□[4]
Step-father/ mother's live-in partner	□[2]	Other	□[5]
Other relative e.g. uncle, grandfather	□[3]	No father figure	□[6]

iii) Your age at start: ..... years

e) Fifth Family Arrangement *(if applicable)*

i) Mother figure:

Natural mother	□[1]	Other non-relative e.g. foster/adoptive/godmother	□[4]
Step-mother/father's live-in partner	□[2]	Other	□[5]
Other relative e.g. aunty, grandmother	□[3]	No mother figure	□[6]

ii) Father figure:

Natural father	□[1]	Other non-relative e.g. foster/adoptive/godfather	□[4]
Step-father/ mother's live-in partner	□[2]	Other	□[5]
Other relative e.g. uncle, grandfather	□[3]	No father figure	□[6]

iii) Your age at start: ..... years

f) Sixth Family Arrangement *(if applicable)*

i) Mother figure:

Natural mother	□[1]	Other non-relative e.g. foster/adoptive/godmother	□[4]
Step-mother/father's live-in partner	□[2]	Other	□[5]
Other relative e.g. aunty, grandmother	□[3]	No mother figure	□[6]

ii) Father figure:

Natural father	□[1]	Other non-relative e.g. foster/adoptive/godfather	□[4]
Step-father/ mother's live-in partner	□[2]	Other	□[5]
Other relative e.g. uncle, grandfather	□[3]	No father figure	□[6]

iii) Your age at start: ..... years

g) Were you ever in a children's home or institution prior to age 17?

i) Yes 0[1] No 0[2]

ii) If **YES**, type of institution:

iii)

Local authority care	□[1]	i) Age entered: ..... years	ii) Age left: ..... years
Hospital	□[2]	i) Age entered: ..... years	ii) Age left: ..... years
Boarding school	□[3]	i) Age entered: ..... years	ii) Age left: ..... years
Other	□[4]	i) Age entered: ..... years	ii) Age left: ..... years
Unknown	□[5]	i) Age entered: ..... years	ii) Age left: ..... years

6.20 Parental Loss and Separation

a) Did either parent die before you were aged 17?

i) Mother: Yes □[1] No □[2]

ii) If **YES**, your age: ..... years

iii) Father: Yes □[1] No □[2]

iv) If **YES**, your age: ..... years

b) Have you ever been separated from either parent for 6 months or more before 17?

i) Mother: Yes □[1] No □[2]

ii) If **YES**, your age at first separation: ..... years

iii) Number of years of separation: ..... years ..... months

iv) Reason for separation from mother:

Parental illness	Yes □[1]	No □[2]
Parental divorce, separation	Yes □[1]	No □[2]
Abandoned by parent or never knew parent	Yes □[1]	No □[2]
Other (please specify below)	Yes □[1]	No □[2]
N/A	□[77]	

Please describe your experience *(not for data entry)*

.....

.....

v) Father: Yes □[1] No □[2]

vi) If **YES**, your age at first separation: ..... years

vii) Number of years of separation: ..... years ..... months

viii) Reason for separation from father:

Parental illness	Yes □[1]	No □[2]
Parental divorce, separation	Yes □[1]	No □[2]
Abandoned by parent or never knew parent	Yes □[1]	No □[2]
Other (please specify below)	Yes □[1]	No □[2]
N/A	□[-77]	

Please describe your experience *(not for data entry)*

.....

.....

6.21 Physical Punishment Before the Age of 17 by a Parent Figure or Other Household Member

a) When you were a child or a teenager were you ever hit repeatedly with an implement (such as a belt or stick) or punched, kicked or burnt by someone in the household?

Yes □[1] No □[2] *(go to 6.22)*

b) How old were you when it began?

i) Mother figure - your age: ..... years
ii) Father figure - your age: ..... years

c) Did the hitting happen on more than one occasion?

i) Mother figure	Yes □[1]	No □[2]
ii) Father figure	Yes □[1]	No □[2]

d) How were you hit by your mother?

i) Belt or stick	Yes □[1]	No □[2]
ii) Punched or kicked	Yes □[1]	No □[2]
iii) Hit with hand	Yes □[1]	No □[2]
iv) Other	Yes □[1]	No □[2]
v) Not applicable	0[-99]	

e) How were you hit by your father?

i) Belt or stick	Yes □[1]	No □[2]
ii) Punched or kicked	Yes □[1]	No □[2]
iii) Hit with hand	Yes □[1]	No □[2]
iv) Other	Yes □[1]	No □[2]
v) Not applicable	□[-99]	

f) Were you ever injured, e.g. bruises, black eyes, broken limbs?

i) Mother figure	Yes □[1]	No □[2]
ii) Father figure	Yes □[1]	No □[2]

g) Was this person ever so angry they seemed out of control?

i) Mother figure	Yes □[1]	No □[2]
ii) Father figure	Yes □[1]	No □[2]

Please describe your experience *(not for data entry)*

.....

.....

h) Did you experience this from anyone else in the household?

i) Sibling	Yes □[1]	No □[2]
ii) Grandparent	Yes □[1]	No □[2]
iii) Uncle/aunt	Yes □[1]	No □[2]
iv) Other	Yes □[1]	No □[2]

Please describe your experience *(not for data entry)*

.....
.....

6.22 Unwanted Sexual Experiences Before Age 17

a) When you were a child or teenager did you ever have any unwanted sexual experiences?

Yes	□[1]	Refused to answer	□[-88]
No	□[2]	Unsure	□[-77]

b) Did anyone force you or persuade you to have sexual intercourse against your wishes before age 17?

Yes	□[1]	Refused to answer	□[-88]
No	□[2]	Unsure	□[-77]

c) Can you think of any upsetting sexual experiences before age 17 with a related adult or someone in authority, e.g. teacher?

Yes	□[1]	Refused to answer	□[-88]
No	□[2]	Unsure	□[-77]

(If **YES** or **UNSURE** [-77] to any of the above then continue)

d) 1st Experience:

i) How old were you when it began? Age: .....years

ii) Was the other person someone you knew?

Yes	□[1]	Refused to answer	□[-88]
No	□[2]	Unsure	□[-77]

iii) Was the other person a relative?

Yes	□[1]	Refused to answer	□[-88]
No	□[2]	Unsure	□[-77]

iv) Did this person do it on more than one occasion?

Yes	□[1]	Refused to answer	□[-88]
No	□[2]	Unsure	□[-77]

v) Did it involve touching private parts of your body?

Yes	□[1]	Refused to answer	□[-88]
No	□[2]	Unsure	□[-77]

vi) Did it involve sexual intercourse?

Yes	□[1]	Refused to answer	□[-88]
No	□[2]	Unsure	□[-77]

Please describe your experience *(not for data entry)*

.....

.....

e) 2nd Experience:

i) How old were you when it began? Age: .....years

ii) Was the other person someone you knew?

Yes	□[1]	Refused to answer	□[-88]
No	□[2]	Unsure	□[-77]

iii) Was the other person a relative?

Yes	□[1]	Refused to answer	□[-88]
No	□[2]	Unsure	□[-77]

iv) Did this person do it on more than one occasion?

Yes	□[1]	Refused to answer	□[-88]
No	□[2]	Unsure	□[-77]

v) Did it involve touching private parts of your body?

Yes	□[1]	Refused to answer	□[-88]
No	□[2]	Unsure	□[-77]

v**i)** Did it involve sexual intercourse?

Yes	□[1]	Refused to answer	□[-88]
No	□[2]	Unsure	□[-77]

Please describe your experience *(not for data entry)*

.....

.....

Reference: Bifulco, A., Bernazzani, O., Moran, P.M., Jacobs, C. (2005). The Childhood Experiences of Care and Abuse Questionnaire (CECA.Q) – validation in a community series. *Br J Clin Psychol, 44*, 563-565

APPENDIX XV – Psychiatric and Personal History Schedule one year Follow-up

PSYCHIATRIC AND PERSONAL HISTORY SCHEDULE
ONE YEAR FOLLOW-UP

Starting
Time:_____

Finishing
Time:_____

Date of interview:

☐☐☐☐☐☐ 1-6

Centre No:

☐☐ 7, 8

Interviewer ID No.

☐☐ 9, 10

Resp. ID No:

☐☐☐☐ 11 - 14

1.1 Date of inclusion (completion of screening schedule)

☐☐☐☐☐☐ 15-20

Day Month Year

1.2 Date of initial evaluation with SCAN

☐☐☐☐☐☐ 21-26

Day Month Year

1.3 Sex of patient

1 = Male
2= Female

☐ 27

1.4 Age of patient (complete with years)

☐☐ 28-29

1.5 Patient died since initial evaluation?

0 = no
1 = yes
9 = no information/not known

☐ 30

If the patient has died since the index episode examination, complete sections 2 through 9 for the period preceding the patient's death, and fill in section 10 of this schedule completely.

1.6 Sources of information used for filling in this schedule

0 = no 1 = yes

☐ 31

1.6.1 Interview with patient

1.6.2 Informant interviews(s)

☐ 32

1.6.3 Case notes from hospital admission or outpatient care since the initial evaluation

☐ 33

1.6.4 Other written documents, specify:_____

☐ 34

1.6.5 Other sources, specify:_____

☐ 35

1.7 List the relationship to the patient (e.g. wife, mother, close friend, etc.) of all informants from whom information was collected and rate the frequency of each informant's contact with the patient

9 = No key informant

1 = High frequency: The informant has direct face-to-face contact with the patient on a daily or almost daily basis over the last four months.

2 = Medium frequency: The informant has had direct face-to-face contact with the patient at least once a week over the past four months.

3 = Low frequency: The informant has direct face-to-face contact with the patient less than once a week over the last four months.

2. MENTAL STATE AND TREATMENT

(To be filled out by project researcher)

2.1 Description of course and progress since initial evaluation

Instruction and coding:

The collection of information for this section of the schedule presupposes certain clinical skills. It should be obtained form either patients or informants, or preferably both. Case notes should be consulted and excerpts made, where relevant. The interview with patient or informant should proceed in the manner usual for a clinical follow-up interview, and the investigator is advised to take notes as he goes along.

To facilitate the recording of information a chart is supplied. Each of the 19 categories should be coded at baseline, at the follow-up (i.e. over the last month), and a global score should be given to describe the whole follow-up period in general. A narrative note should be made to summarise the presence of change in intensity of symptoms, as well as the general behaviour of the patient and any relevant happenings. If no information is available the investigator should write in 'no information'.

Generally, code 0 = absent should be used when the investigator finds that the symptoms belonging to a particular category (e.g. hallucinations) were definitely not present during the follow-up. With some exceptions where this is specifically indicated. The codes 1 = mild or occasional and 2 = severe or frequent, are used to denote the intensity of symptoms, in a manner consistent with the SCAN. A difference which should be borne in mind, however, is that in the present schedule symptomatology is assessed on a more general level than in the SCAN, and the codes refer to groups of symptoms rather than to individual symptoms. Therefore, the ratings should reflect a more global judgement about several items. Code 2 should be used sparingly and reserved for cases where many of the symptoms belonging to one group have been present during a particular period, or more rarely when 1-2 symptoms have been present with marked intensity. If the presence of a symptom cannot be excluded but not clear evidence is available, or if the investigator has reasons to suspect that it was present, code 9 = uncertain should be used.

MENTAL STATE AND TREATMENT

MENTAL STATE	AT INDEX	AT FOLLOW-UP	TOTAL FOLLOW-UP PERIOD	NARRATIVE Mental State, General Behaviour	Treatment
1. Delusions					
2. Hallucinations					
3. Thought Disorder					
4. Psychomotor Disorder					
5. Flatness of Affect					
6. Apathy					
7. Social Withdrawal					
8. Odd Behaviour					
9. Self Neglect					
10. Affective Symptoms					
11. Anxiety					
12. Other Symptoms					
TREATMENT					
13. No of Days in Institution					
14. Outpatient Management					
15. Drugs					
16. Compliance					
17. Other Biological Treatment					
18. Psycho Socio-Therapy					
19. Traditional Treatment					

Note: Use Narrative boxes to record as much details as possible (e.g. has person been continuously ill or had a number of episode etc.)

2.1.1 DELUSIONS: Included are all varieties, as defined in the SCAN Glossary

Delusions of control
- reference
- thoughts being read
- thoughts being withdrawn
- thoughts being broadcast

Delusional misinterpretations and mis-identifications

Delusions of persecution
- assistance
- grandiose abilities
- grandiose identity
- religious Delusions

Delusional explanations of other abnormal feelings

Delusions of alien forces penetrating or Controlling mind or body
Delusional jealousy
Delusions of pregnancy
Sexual Delusions
Delusional memories and confabulations
Fantastic delusions
Delusions of guilt
Delusions concerning appearance
Delusions of depersonalization
Hypochondriacal delusions
Delusions of catastrophe
Delusion that subject smells

Codes 0,1,2 and 9 (see above)

☐ 46

2.1.2 HALLUCINATIONS: Included are

Non-Verbal Auditory Hallucinations
Verbal Auditory "

Note: Pseudo Hallucinations (i.e. hallucinatory experiences which the subject locates in his inner, subjective space – e.g. voices within his own mind) are also included. Excluded illusions (I.e. falsified perceptions of real objects).

Visual "
Olfactory "
Tactile "
Gustatory "
Sexual "
Any other Hallucinations
Codes 0,1,2 and 9

☐ 47

2.1.3 THOUGHT (AND SPEECH) DISORDER

Includes:

Irrelevance
Speech dissociation
Blocking
Echolalia
Neologisms
Clang associations
Flights of ideas

Codes 0,1,2 and 9

☐ 48

2.1.4 PSYCHOMOTOR DISORDER: Includes

Stupor	Stereotypes
Severe excitement	Negativism
Mutism	Mannerism
Posturing	Compliance
Waxy flexibility	Marked over-activity and restlessness

Codes 0,1,2 and 9

☐ 49

2.1.5 FLATNESS OF AFFECT:

Rate as present only if clear evidence is available of uniform blunting of affect and general lack of emotional response.

Codes 0,1,2 and 9

☐ 50

2.1.6 APATHY:

General diminution or lack of interest, initiative and drive.

Note: Include here extreme slowness and doing nothing.

Codes 0,1,2 and 9

☐ 51

2.1.7 SOCIAL WITHDRAWAL:

(I) Less intense form - Subject does not seek company but does not refuse it when offered.

(II) More intense form - Subject actively withdraws and refuses company even when it is offered.

Codes 0,1,2 and 9

☐ 52

2.1.8 ODD BEHAVIOUR: Includes

Talking or muttering to self
Bizarre appearance
Disregard for social norms and conventions
Codes 0,1,2 and 9

☐ 53

2.1.9 SELF-NEGLECT: Marked lack of attention to

Personal cleanliness
State of hair
Note: Do not include simple untidiness
Codes 0,1,2 and 9

Clothes
Make-up etc.

☐ 54

2.1.10 AFFECTIVE SYMPTOMS:

(a) Manic:
Elated Mood
Over-activity
Accelaration of thought and speech

Manic delusions and severe thought disorders (flight of ideas) should be rated under

Code:

☐ 55

1 = mild or less than 50% of the time
2 = severe or more than 50% of the time

(b) Depressive:
Depression of mood
Retardation
Lack of appetite and libido
Characteristic disturbance of sleep (e.g. early wakening)
Gloomy thoughts

Suicidal thoughts

Code:

☐ 56

4 = mild or less than 50% of the time
5 = severe or more than 50% of the time

2.1.11 ANXIETY AND EXCESSIVE WORRYING: Icludes

(a) Anxiety:

Feeling anxious

Feeling (not delusion) that something terrible is going to happen
Phobic fears of particular objects or environments
Panic attacks
Autonomic nervous system accompaniments of anxiety

☐ 57

(b) Worrying:

Persisting painful unpleasant thoughts which cannot be stopped voluntarily are out of proportion to the subject worried about.

☐ 58

1 = mild or less than 50% of the time
2 = severe or more than 50% of the time

4 = mild or less than 50% of the time
5 = severe or more than 50% of the time

2.1.12 OTHER SYMPTOMS:

Although several may be present at the same time, choose one code to record the symptom(s) which have been most severe or distressing during the follow-up period

☐ 59

Codes:
0 = None
1 = Persistent insomnia
2 = Hypersomnia
3 = Other disturbances of appetite (not simple lack)
4 = Hostility, aggressiveness
5 = Obsessive ideas and behaviour
6 = Hypochondriasis
7 = Dyskinesia, muscle rigidity and other side effects
9 = Uncertain

2.1.13 CODES FOR TREATMENT ITEMS:

Number of days in institution:
Includes inpatient treatment in psychiatric hospital or any other institution to which the patient has been admitted because of mental disorder. Do not code here hospitalization unrelated to mental disorder. Code 88 if the patient was in an institution during the follow-up period but the number of days is not know even approximately. Code 00 if the patient was not in an institution during the month.

☐ 60

2.1.14 OUTPATIENT MANAGEMENT:

Includes out patient attendances, domiciliary visits by health service staff or social worker, day hospital and rehabilitation centre attendance.

☐ 61

Codes:
0 = None
1 = Outpatient attendance and/or domiciliary visits, patients seen by service staff not more than twice during the follow-up period.
2 = As above, but patient seen 3 or more times during the follow-up period.
3 = Day hospital or rehabilitation centre attendance, less than 50% of the time during the follow-up period.
4 = As above, but more than 50% of the time during follow-up period.
5 = Combination of either 1 or 2 with 3.
6 = Combination of either 1 or 2 with 4.
8 = Not applicable, patient was in institution throughout the follow-up period.
9 = Not know.

2.1.15 DRUGS:

Code drugs which were prescribed or given to the patient (regardless of his compliance)

☐ 61

Codes:
0 = None
1 = Conventional neuroleptics (oral or injectable) of any chemical structure.
2 = Long-acting (depot) neuroleptics or combination of a long-acting and ordinary neuroleptics.
3 = Antidepressants
4 = Minor tranquillizers
5 = Combination of antidepressants and minor tranquillizers
6 = Combination of neuroleptics and antidepressants
7 = Lithium
8 = Novel antipsychotic drugs (Clozapine, Risperidone, Olanzapine, Quetiapine, Amisulpride, Sertindole)
9 = Neuroleptics and tranquillizers
10 = Novel antipsychotic and tranqullizers
11 = Novel antipsychotic and antidepressants
12 = Other combination, Specify
_____

2.1.16 COMPLIANCE WITH DRUG TREATMENT:

Assess the extent to which the patient has followed the instructions given to him with regard to the prescribed treatment, especially as concerns regularity of intake and dosage.

☐ 63

Codes:
0 = Drugs taken regularly and in adequate dosage.
1 = Drugs taken irregularly (with lapses for at least 3 days occurring more than once) or in an inadequate dosage (too low).
2 = Drugs prescribed but probably not taken at all.
8 = Not applicable, no drug treatment during the month.
9 = Uncertain, no information available.

2.1.17 OTHER BIOLOGICAL TREATMENT:

☐ 64

Codes:
0 = None
1 = Electroconvulsive treatment (ECT) not more than 2 within the month.
2 = ECT, 3 or more within the month
3 = Insulin coma treatment
4 = Combination of ECT and insulin coma treatment
5 = Other biological treatment
9 = Uncertain, no information available

2.1.18 PSYCHOTHERAPY OR SOCIO-THERAPY:

Includes individual and group techniques utilizing interpersonal interaction between therapist and patient , or between a particular social environment and patient, as in the main approach toward a specified therapeutic goal. Simple “talking with the patient” does not qualify, unless it meets the above criteria.

☐ 65

Codes:
0 = None
1 = Counselling and similar supportive measures
2 = Individual psychotherapy
3 = Group psychotherapy
4 = Family or couple therapy
5 = Occupational therapy (excludes industrial rehabilitation, vocational retraining, sheltered work, etc.)
6 = Industrial rehabilitation or vocational retraining.
7 = Other or unspecified psycho- or socio-therapy.

2.1.19 TRADITIONAL TREATMENT:

A great variety of traditional healing practices exists and the particular form applied should be described in a narrative. ☐ 66

Codes:
0 = None
1 = Ambulatory traditional treatment
2 = Residential traditional treatment
9 = Uncertain

2.2 CURRENT MENTAL STATE:

☐ 67

Is the patient now (last 30 days) in a psychotic episode? (see Appendix 1, this schedule)

0 = No.
1 = Yes, still in episode of inclusion
2 = Yes, but not contiguous with episode in inclusion
8 = Impossible to assess, specify reason:_____
9 = No information/no known

2.3 REMISSION:

☐ 68

a) Has the patient had a remission of psychotic symptoms (See Appendix 1, this schedule) for a period of at least 30 days since the initial evaluation?

0 = No
1 = Yes
8 = Impossible to assess, specify reason:_____

☐☐☐ 69-71

b) If YES above (2.3), for how many weeks was the patient in the episode of inclusion – i.e., the number of weeks from the first onset of psychosis symptoms until the beginning of the patient's first remission (888 = patient still in episode of inclusion; 999 = no information/not know)

2.4 RELAPSE EPISODE:

☐☐ 72-73

How many discrete psychotic episode (not including the episode of inclusion) has the patient had since the initial evaluation? (Each "psychotic episode" must be separated by at least 30 days spent in remission)

00 = Patient presently in remission form episode of inclusion
88 = Patient still in episode of inclusion
99 = Not know/impossible to access

2.4.1 Please record length of each discrete episode

_____
_____
_____

2.5 CURRENT TREATMENT STATUS:

Patient's treatment status at the time of this examination. ☐ 74

0 = Not in any form of treatment
1 = Inpatient in medical psychiatric facility (includes general hospital psychiatric wards)
2 = Outpatient in a psychiatric or rehabilitation service
3 = Partial hospitalization in a medical psychiatric facility (e.g. day hospitalization, etc.)
4 = Under ambulatory treatment from a religious or traditional healer
5 = Partial or complete confinement in a traditional or religion healing facility or compound
6 = Other, specify:_____
_____
7 = More than one above, specify: _____
_____
9 = No information/not know

2.6 PATTERN OF COURSE:

☐ 75

Which of the following patterns of course best describe the patient's condition since the initial evaluation?

0 = Complete or nearly complete recovery without relapses or exacerbations of psychotic symptoms
1 = No relapses or exacerbations of psychotic symptoms but with residual personality change
2 = One or more relapses or acute exacerbations of psychotic symptoms, with full or nearly full remissions following them with no marked personality change
3 = One or more relapses or exacerbations of psychotic symptoms against a background of marked personality change
4 = Continuous psychotic illness
7 = Other, specify
:_____
_____
9 = Impossible to assess/not know.

2.7 If a continuous illness please rate fluctuations:

☐ 76

1 = Minimal or none
2 = Medium
3 = Large

5. MARRIAGE, HOUSEHOLD AND FAMILY

☐ 158

5.1 Marital status

Rate any changes in the patient's marital status since the index episode examination.

0 = No change
1 = Married or common law marriage
2 = Engaged to be married or marriage arranged for future date
3 = Broken engagement or marriage arrangement
4 = Divorced
5 = Separated
6 = Widowed
7 = Other, specify:_____
_____
8 = More than one above, specify:_____
_____
9 = No information/not known

5.2 Overall change of socioeconomic level

☐ 159

Rate the overall change in the socioeconomic level of the patient's household since the index episode evaluation. (This item should also be scored for patients who are currently hospitalized).
0 = No change, about the same
1 = Change for the better
2 = Change for the worse
7 = Impossible to assess
8 = Not applicable (e.g. patient has no household of his her own)
9 = No information/not known

5.2a If a change has occurred in the socioeconomic standing of the patient's household since the Index episode examination (i.e. 1 or 2 above), describe the nature and the extent of the change:

_____

_____

6. LIVELIHOOD/OCCUPATION

6.1 Current employment status (last 30 days)

☐ 160

Has the patient been employed at a paid job (i.e. an earning occupation) in the last 30 days?
0 = no
1 = Yes
9 = No information/not known

6.2 Reasons for current unemployment

☐ 161

If the patient has not had a paying job in the last 30 days, rate the reason for unemployment
0 = Student
1 = Housewife
2 = Worker in unpaid family concern (e.g. family farm, etc.)
3 = The patient's mental illness (includes hospitalization, simple refusal to work etc.)
4 = Physical disability or illness
5 = General employment situation
6 = More than one above, specify:

_____

_____

7 = Other, specify:

_____

_____

8 = Not applicable
9 = No information/not known

6.3 Main Occupation

☐☐ 162-163

00 = Retired/pensioner
01 = Agricultural worker – self employed
02 = Agricultural worker – employed or paid in kind
03 = Craftsman, artisan, etc. (self-employed, employed, or member of a cooperative)
04 = Industrial worker – skilled (e.g. foreman)
06 = Clerical or administrative occupation – unskilled or semiskilled (e.g. messenger)
07 = Clerical or administrative occupation – skilled (e.g. secretary)
08 = Service – trade occupation – unskilled or semiskilled (e.g. street vendor, shop assistant)
09 = Service or trade occupation – skilled (e.g. nurse)
10 = Owner of business employing more than 10 people
12 = Professional (e.g. doctor), high-level executive or administrator
13 = Military (officer rank)
14 = Housewife/house-husband
15 = Unemployed
16 = Student
17 = Other
88 = Not applicable
99 = Not known
Specify occupation:_____

6.4 Employment

☐ 164

Rate employment (or earning job) since index episode evaluation (exclude last 30 days)
0 = Has experienced one or more periods of unemployment lasting one month or more
1 = Has been working practically all the time
8 = Not applicable, patient never had a paid job
9 = Not known

6.5 Unemployment

☐ 165

Rate reason for unemployment since index episode evaluation (excluding last 30 days)
0 = Patient's mental illness
1 = Physical illness or disability
2 = General employment situation (specify):
_____
_____
3 = Other (specify):
_____
4 = Combination of the above (specify):
_____
_____
8 = Not applicable, patient was not unemployed
9 = Not known

6.6 Conditions of work

☐ 166

Rate conditions of work since the index episode evaluation.
0 = Full-time only, normal conditions
1 = Full-time only, sheltered conditions
2 = Part-time only, normal conditions
3 = Part-time only, sheltered conditions
4 = Some full and some part-time, normal conditions
5 = Some full and some part-time, normal conditions
6 = Combination of the above, specify:_____
_____
_____
7 = Other, specify:_____
_____
_____
8 = Not applicable
9 = No information not known

6.7 Job changes

☐ 167

Rate the number of job changes by the patient since the index episode examination
0 = No change of jobs
7= Patient full-time student, housewife, or unpaid worker in family concern, or holds other alternative status
8 = Not applicable, continuously hospitalized since index episode examination, patient does not work, etc.
9 = No information/not known

6.8 Levels of earned income

☐ 168

Rate changes in the patient's level of earned income since the index episode evaluation. (Rate this item by comparing the levels of income earned from the patient's main occupation before and after the index episode evaluation).
0 = No change, about the same
1 = Some improvement (less than 20% increase)
2 = Marked improvement (more than 20% increase)
3 = Some decline (less than 20% decline)
4 = Marked decline (more than 20% decline)
8 = Not applicable
9 = Not known/no information

6.9 Housework

☐ 169

Has the patient been doing any housework (e.g. cooking, cleaning, shopping, child-rearing, etc.) since the previous interviewer? (Rate for all patients, male and female).
0 = No
1 = Helps out around house when needed
2 = Has a number of regular assigned tasks
3 = Works full or almost full-time at housework
8 = Not applicable (e.g. continuously hospitalized)
9 = No information not known

APPENDIX

ONE YEAR FOLLOW-UP PSYCHIATRIC AND PERSONAL HISTORY SCHEDULE

THE OPERATIONAL DEFINITION OF A PSYCHOTIC EPISODE

Since this concept is central to several key aspects of the study (e.g. the assessment of course and outcome, the testing of hypotheses about impact of life events or emotional expression) it was considered important to agree on a standard operational definition. According to this definition, a psychotic episode is a period of symptomatology in which the presence of at least one of the following symptoms listed in Section C of the Screening Schedule can be ascertained:

(i) Hallucinations or Pseudo hallucinations (any modality)

(ii) Delusions

(iii) Marked thought and speech disorder other than simple retardation or acceleration

(iv) Qualitative (e.g. catatonic) psychomotor disorder, other than simple retardation or acceleration

(v) Emerge or marked exacerbation of bizarre and grossly inappropriate behaviour strongly suggestive of presence of hallucinations or delusions (e.g. talking or giggling to self)

A psychotic episode may be considered at present also in the absence of the manifest symptoms listed above if at least two of the following behaviours listed in Section D of the Screening Schedule have emerged or become markedly exacerbated:

(a) Severe loss of interests, initiative and drive leading to a serious deterioration of performance of usual activities and tasks.

(b) Emergence or marked exacerbation of social withdrawal

(c) Severe excitement, destructiveness or aggression

(d) States of overwhelming fear

(e) Gross and persistent self-neglect

If none of the manifest psychotic symptoms (I) – (v) can be ascertained but on grounds of presence of two or more of the behaviours listed under (a) – (e), or for any other reason the investigator considers the patient to be in a psychotic episode, he should state clearly the reasons for his clinical judgement. In cases where the patient is on anti-psychotic medication, and does not exhibit any of the symptoms or behaviours listed above but the

investigator suspects that withdrawal of medication would reveal presence of psychotic symptoms, the patient should not be considered to be in a psychotic episode.

In order to qualify as a psychotic **episode**, the above symptomatology must be preceded or followed by a period of at least 30 days during which the symptoms and behaviour described above were **absent** (see operational definition of remission). The general rule concerning the rating of psychotic episodes should be:

- to rate **conservatively** (i.e. give the patient "the benefit of the doubt")
- to base one's judgement **predominantly** on ascertainable **qualitative** chance in the patient's mental state.

THE OPERATIONAL DEFINITION OF A "REMISSION"

A remission (or interval) is a state following a psychotic episode, in which none of the symptoms listed as characterised of a psychotic episode are present. During a remission a patient may exhibit a variety of non-psychotic symptoms (e.g. depressed mood, neurotic manifestations) or some of the so-called "negative" symptoms, or be entirely symptom-free (incomplete or complete remission). A rating of remission (as well as a rating of a psychotic episode) should be based only on a ascertainable absence (or presence) or psychotic symptoms and not on whether the patient is taking any psychotropic medication or not, or whether he is hospitalized or not. The absence of psychotic symptomatology would qualify as a remission only if its lasts for **30 days or more**.

Reference: Sartorius, N., Jablensky, A., Korten, A., Ernberg, G., Anker, M., Cooper, J.E., Day, R. (1986). Early manifestations and first-contact incidence of schizophrenia in different cultures. A preliminary report on the initial evaluation phase of the WHO Collaborative Study on determinants of outcome of severe mental disorders. *Psychol Med*, *16 (4)*, 909–928.

APPENDIX XVI- Correlation matrices of types of childhood adversities

Table S1. Phi correlation analysis of types of adversities in first-episode psychosis patients (n= 285)

	1	2	3	4	5	6	7
1. Parental Separation	1.000						
2. Parental loss	0.012						
3. Physical Abuse	0.075	-0.017					
4. Sexual Abuse	0.098	-0.054	0.206**				
5. Institutional care	0.101	0.170**	0.070	0.092			
6. Disrupted Family arrangements	0.358**	0.183**	0.123*	0.128*	0.355**		
7. Any Adversity	0.713**	0.234**	0.345**	0.261**	0.144*	0.322**	1.000

* P < 0.05. ** P < 0.01.

Table S2. Phi correlation analysis of types of adversities in unaffected controls (n= 256)

	1	2	3	4	5	6	7
1. Parental Separation	1.000						
2. Parental loss	0.111						
3. Physical Abuse	0.190**	-0.103					
4. Sexual Abuse	0.083	0.025	0.059				
5. Institutional care	0.131*	-0.37	0.097	0.041			
6. Disrupted Family arrangements	0.460**	0.213**	0.229**	-0.010	0.290**		
7. Any Adversity	0.737**	0.262**	0.436**	0.360**	0.143*	0.375**	1.000

* P < 0.05. ** P < 0.01.

APPENDIX XVII - Association between childhood adversity and relationship status at 12 months follow-up

Type of childhood adversity	In Relationship n (%)	Not in a relationship n (%)	Unadjusted OR	95% CI	*P*	Adjusted OR*	95% CI	*P*
Parental separation								
No (n=88)	29 (33.0)	59 (67.0)	1.0	-	-	-	-	-
Yes (n=116)	29 (25.0)	87 (75.0)	1.47	0.80-2.72	0.213	1.11	0.52-2.35	0.760
Parental loss								
No (n=181)	52 (28.7)	129 (71.3)	1.0	-	-	-	-	-
Yes (n=22)	7 (31.8)	15 (68.2)	0.86	0.33-2.24	0.763	0.83	0.26-2.62	0.747
Physical abuse								
No (n=159)	49 (30.8)	110 (69.2)	1.0	-	-	-	-	-
Yes (n=47)	10 (21.3)	37 (78.7)	1.65	0.76-3.58	0.207	**2.67**	0.96-7.44	**0.060**
Sexual abuse								
No (n=174)	53 (30.5)	121 (69.5)	1.0	-	-	-	-	-
Yes (n=32)	6 (18.8)	26 (81.3)	1.90	0.74-4.88	0.184	1.29	0.44-3.79	0.638
Institutional care								
No (n=196)	57 (29.1)	139 (70.9)	1.0	-	-	-	-	-
Yes (n=10)	2 (20.0)	8 (80.0)	1.64	0.34-7.96	0.539	1.70	0.28-10.19	0.562
Family arrangements								
Up to 2 (n=156)	44 (28.2)	112 (71.8)	1.0	-	-	-	-	-
3 or more (n=43)	14 (32.6)	29 (67.4)	0.81	0.39-1.68	0.578	1.04	0.41-2.63	0.930

*Adjusted for T0 relationship status. CI, confidence interval. OR, odds ratio.

APPENDIX XVIII - Association between childhood adversity and employment status at 12 months follow-up

Type of childhood adversity	Employed n (%)	Not employed n (%)	Unadjusted OR	95% CI	*P*	Adjusted OR*	95% CI	*P*
Parental separation								
No (n=87)	25 (28.7)	62 (71.3)	1.0	-	-	-	-	-
Yes (n=113)	22 (19.5)	91 (80.5)	1.67	0.86-3.22	0.127	1.17	0.55-2.48	0.680
Parental loss								
No (n=179)	40 (22.3)	139 (77.7)	1.0	-	-	-	-	-
Yes (n=20)	7 (35.0)	13 (65.0)	0.53	0.20-1.43	0.212	0.52	0.17-1.61	0.260
Physical abuse								
No (n=159)	40 (25.2)	119 (74.7)	1.0	-	-	-	-	-
Yes (n=43)	8 (18.6)	35 (81.4)	1.47	0.63-3.43	0.372	1.75	0.66-4.62	0.259
Sexual abuse								
No (n=170)	42 (24.7)	128 (75.3)	1.0	-	-	-	-	-
Yes (n=32)	6 (18.8)	26 (81.3)	1.42	0.55-3.69	0.469	1.26	0.44-3.59	0.662
Institutional care								
No (n=192)	44 (22.9)	148 (77.1)	1.0	-	-	-	-	-
Yes (n=10)	4 (40.0)	6 (60.0)	0.45	0.12-1.65	0.227	0.38	0.09-1.71	0.209
Family arrangements								
Up to 2 (n=154)	40 (26.0)	114 (74.0)	1.0	-	-	-	-	-
3 or more (n=41)	8 (19.5)	33 (80.5)	1.45	0.62-3.40	0.395	1.34	0.52-3.44	0.544

*Adjusted for T0 employment status. CI, confidence interval. OR, odds ratio.